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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	5/1213
Total Pages	212
First Named Inventor or Application Identifier	Hauel, Norbert; et al
Express Mail Label No.	EM 507234131US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: **Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231**

1. [X] Fee Transmittal Form *(Submit an original, and a duplicate for fee processing)*
2. [X] Specification [*Total Pages* 203] *(preferred arrangement set forth below)*
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) *(35 USC 113)* [*Total Sheets*]
4. Oath or Declaration [*Total Pages*]
   - a. [XX] Newly executed (original or copy)
   - b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)* ***[Note Box 5 below]***
     - i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
5. [ ] Incorporation By Reference *(useable if Box 4b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program *(Appendix)*
7. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   - a. [ ] Computer Readable Copy
   - b. [ ] Paper Copy (identical to computer copy)
   - c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [XX] Assignment Papers (cover sheet & document(s))
9. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [XX] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [XX] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
14. [ ] Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [ ] Other: .....

17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information:*
    ☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____/_____

18. CORRESPONDENCE ADDRESS

☐ *Customer Number or Bar Code Label* *(Insert Customer No. or Attach bar code label here)* or ☐ *Correspondence address below*

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FEE TRANSMITTAL

Note: Effective October 1, 1997.
Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 2468.00

Complete if Known	
Application Number	
Filing Date	
First Named Inventor	Hauel, Norbert; et al
Group Art Unit	
Examiner Name	
Attorney Docket Number	5/1213

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to.

Deposit Account Number: 02=2955
Deposit Account Name:

[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17
[ ] Charge the Issue Fee Set in 37 CFR 1.18 at the Mailing of the Notice of Allowance

2. [ ] Payment Enclosed: [ ] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	790.00
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 790.00

2. CLAIMS

		Extra		Fee from below		Fee Paid
Total Claims	71 -20 =	51	X	22	=	1122
Independent Claims	6 - 3 =	3	X	82	=	246
Multiple Dependent Claims		1	X	270	=	270

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim
109	82	209	41	Reissue independent claims over original patent
110	22	210	11	Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 1638

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,320	241	660	Petition to revive - unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	40
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 40.00

SUBMITTED BY

				Complete (if applicable)	
Typed or Printed Name	Alan R. Stempel			Reg. Number	28,991
Signature	Alan Stempel	Date	2/18/98	Deposit Account User ID	

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DISUBSTITUTED BICYCLIC HETEROCYCLES, THE PREPARATION AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS

Reference to Prior Provisional Application

Benefit of prior filed and copending U.S. provisional application Serial Number 60/044,421, filed on April 29, 1997, is hereby claimed.

Description of the Invention

The present invention relates to new disubstituted bicyclic heterocycles of general formula

$$R_a - A - Het - B - Ar - E \quad ,(I)$$

the tautomers, stereoisomers and mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases which have valuable properties.

The compounds of general formula I above wherein E denotes a cyano group are valuable intermediates for preparing the other compounds of general formula I, and the compounds of general formula I above wherein E denotes an $R_bNH-C(=NH)-$ group, and the tautomers and stereoisomers thereof have useful pharmacological properties, particularly a thrombin-inhibiting activity and the effect of extending thrombin time.

The present application thus relates to the new compounds of general formula I above and the preparation thereof, pharmaceutical compositions containing the pharmacologically active compounds and the use thereof.

In the above general formula

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, wherein a methylene group, linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-6}-alkyl group,

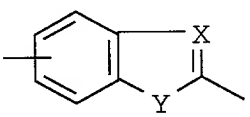
E denotes a cyano or $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3}-alkyl group or a group which may be cleaved *in vivo*,

Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

Het denotes a bicyclic heterocycle of formula



, wherein

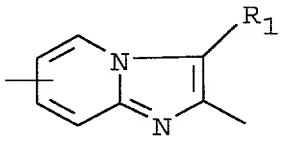
X is a nitrogen atom and

Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R_1, wherein R_1 is as hereinbefore defined, and

Y denotes a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group,

or Het denotes a group of the formula



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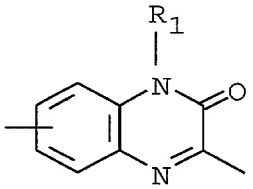

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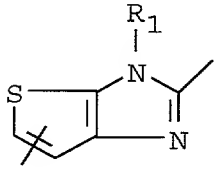

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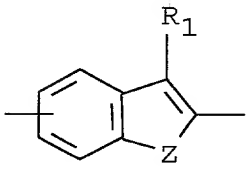

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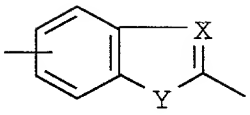
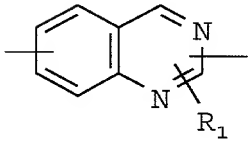


or



, wherein

R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or an R_2NR_3- group wherein

R_2 denotes a C_{1-4}-alkyl group, which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C_{2-4}-alkyl group substituted by a hydroxy, phenyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups

the carbon atom in the α-position relative to the adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a C_{1-3}-alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, a C_{3-6}-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3- group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl or imidazolyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or C_{1-4}-alkoxycarbonyl group, onto which a phenyl ring may additionally be fused.

The compounds of the above general formula I which contain a group capable of being cleaved *in vivo* are thus prodrugs and compounds of general formula I which contain two groups capable of being cleaved *in vivo* are so-called double prodrugs.

The phrase "a group which may be converted *in vivo* into a carboxy group" denotes, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol, in which the alcoholic moiety is preferably a C_{1-6}-alkanol, a phenyl-C_{1-3}-alkanol, a C_{3-9}-cycloalkanol, wherein a C_{5-8}-cycloalkanol may additionally be substituted by one or

two C_{1-3}-alkyl groups, a C_{5-8}-cycloalkanol, in which a methylene group in the 3- or 4-position is replaced by an oxygen atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl-C_{1-3}-alkyl, phenyl-C_{1-3}-alkoxycarbonyl or C_{2-6}-alkanoyl group, and the cycloalkanol moiety may additionally be substituted by one or two C_{1-3}-alkyl groups, a C_{4-7}-cycloalkenol, a C_{3-5}-alkenol, a phenyl-C_{3-5}-alkenol, a C_{3-5}-alkynol or phenyl-C_{3-5}-alkynol, with the proviso that no bond to the oxygen atom emanates from a carbon atom which carries a double or triple bond, a C_{3-8}-cycloalkyl-C_{1-3}-alkanol, a bicycloalkanol having a total of 8 to 10 carbon atoms, which may additionally be substituted in the bicycloalkyl moiety by one or two C_{1-3}-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

$$R_4\text{-}CO\text{-}O\text{-}(R_5CR_6)\text{-}OH,$$

wherein

R_4 denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_5 denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_6 denotes a hydrogen atom or a C_{1-3}-alkyl group,

or the phrase "a group which may be cleaved *in vivo* from an imino or amino group" denotes for example a hydroxy group, an acyl group such as a benzoyl- or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl-, acetyl-, propionyl-, butanoyl-, pentanoyl- or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl-, ethoxycarbonyl-, propoxycarbonyl-, isopropoxycarbonyl-, butoxycarbonyl-, tert.-butoxycarbonyl-, pentoxycarbonyl-, hexoxycarbonyl-, octyloxycarbonyl-, nonyloxycarbonyl-, decyloxycarbonyl-,

undecyloxycarbonyl-, dodecyloxycarbonyl- or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl-, phenylethoxycarbonyl- or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl-, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl- or R_4CO-O-(R_5CR_6)-O-CO-group, wherein R_4 to R_6 are as hereinbefore defined.

Examples of preferred prodrug groups for a carboxy group include a C_{1-6}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl or cyclohexyloxycarbonyl group or phenyl-C_{1-3}-alkoxycarbonyl group such as the benzyloxycarbonyl group and

for an imino or amino group a C_{1-9}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, n-propyloxycarbonyl, isopropyloxycarbonyl, n-butyloxycarbonyl, n-pentyloxycarbonyl, n-hexyloxycarbonyl, cyclohexyloxycarbonyl, n-heptyloxycarbonyl, n-octyloxycarbonyl or n-nonyloxycarbonyl group, a phenyl-C_{1-3}-alkoxycarbonyl group such as the benzyloxycarbonyl group, a phenylcarbonyl group optionally substituted by a C_{1-3}-alkyl group such as the benzoyl or 4-ethyl-benzoyl group, a pyridinoyl group such as the nicotinoyl group, a C_{1-3}-alkylsulphonyl-n-C_{2-3}-alkoxycarbonyl or C_{1-3}-alkoxy-C_{2-3}-alkoxy-C_{2-4}-alkoxycarbonyl group such as the 2-methylsulphonylethoxycarbonyl or 2-(2-ethoxy)-ethoxycarbonyl group.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms as well as alkanoyl and unsaturated alkyl moieties containing more than 3 carbon

atoms as mentioned in the foregoing definitions also include the branched isomers thereof such as for example the isopropyl, tert.-butyl and isobutyl group, etc.

Preferred compounds of the above general formula I, however, are those wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, in which a methylene group, linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-5}-alkyl group,

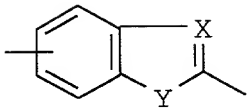
E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3}-alkyl group or a group which may be cleaved *in vivo*,

Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

Het denotes a bicyclic heterocycle of formula



, wherein

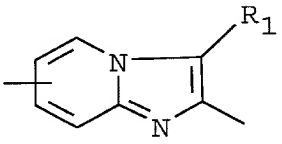
X is a nitrogen atom and

Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R_1, wherein R_1 is as hereinbefore defined, and

Y denotes a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group,

or Het denotes a group of the formulae



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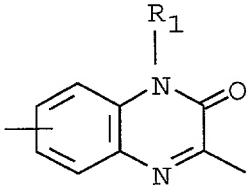

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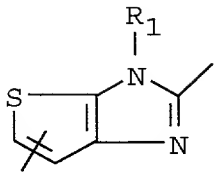

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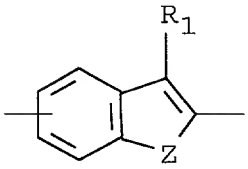

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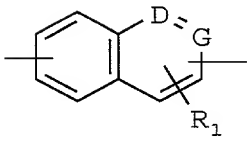
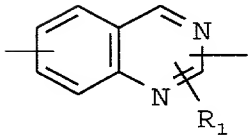


or



, wherein

R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or a R_2NR_3- group wherein

R_2 denotes a C_{1-4}-alkyl group, which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C_{2-4}-alkyl group substituted by a hydroxy, phenyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position relative to the adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a C_{1-3}-alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, a C_{3-6}-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3- group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl or piperidinyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C_{1-4}-alkoxycarbonyl group, onto which a phenyl ring may additionally be fused, particularly those compounds wherein

Het denotes one of the abovementioned benzimidazolylene, benzothiazolylene, benzoxazolylene, indolylene, quinazolinylene, quinoxazolinonylene, imidazo[4,5-b]pyridinylene, imidazo[1,2-a]pyridinylene, thiazolo[5,4-b]pyridinylene or thieno[2,3-d]imidazolylene groups,

the tautomers, the prodrugs, the double prodrugs, the stereoisomers and the salts thereof.

Particularly preferred compounds of general formula I above are those wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-4}-alkyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl-C_{1-3}-alkoxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or pyridinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a C_{1-3}-alkyl-sulfonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group or it denotes a 2,5-thienylene group,

Het denotes a 1-(C_{1-3}-alkyl)-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-(C_{1-3}-alkyl)-2,5-indolylene, 1-(C_{1-3}-alkyl)-2,5-imidazo[4,5-b]pyridinylene, 3-(C_{1-3}-alkyl)-2,7-imidazo[1,2-a]pyridinylen or 1-(C_{1-3}-alkyl)-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R_2NR_3- group wherein

R_2 is a C_{1-4}-alkyl group substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-4}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted,

R_3 denotes a C_{3-7}-cycloalkyl group, a propargyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, a pyrazolyl, pyridazolyl or pyridinyl group optionally substituted by a methyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C_{1-4}-alkoxycarbonyl group, to which a phenyl ring may additionally be fused,

the tautomers, the stereoisomers and the salts thereof.

Most particularly preferred compounds of the above general formula I are those wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group, wherein

R_b denotes a hydrogen atom or a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a C_{1-3}-alkylsulphonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group, or it denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene, 1-methyl-2,5-imidazo[4,5-b]pyridinylene, 3-methyl-2,7-imidazo[1,2-a]pyridinylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes a R_2NR_3- group wherein

R_2 denotes a C_{1-3}-alkyl group which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-3}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted, and

R_3 denotes a propargyl group, wherein the unsaturated moiety may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, or denotes a pyridinyl group,

particularly those wherein

A denotes a carbonyl group linked to the benzo or thieno moiety of the group Het,

B denotes an ethylene group wherein the methylene group attached to the group Ar may be replaced by an -NR_1 group,

wherein

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b is a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a methylsulfonyl or 2-ethoxy-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a methoxy group, or denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R_2NR_3- group wherein

R_2 denotes a C_{1-3}-alkyl group which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-3}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted, and

R_3 denotes a phenyl group optionally substituted by a fluorine atom, or denotes a 2-pyridinyl group,

the tautomers, stereoisomers and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

(a) 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,

(b) 2-[N-(4-midinophenyl)-N-methyl-aminomethyl]-benzthiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(c) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide,

(e) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,

(f) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(g) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(h) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(i) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(j) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,

(k) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,

(l) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(m) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(n) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(o) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide,

(p) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,

(q) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,

(r) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(s) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and

(u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

the tautomers, prodrugs, double prodrugs, stereoisomers and the salts thereof.

The new compounds may be prepared by methods known *per se*, for example by the following methods:

a. In order to prepare a compound of general formula I, wherein E denotes an $R_bNH-C(=NH)-$ group, wherein R_b is a hydrogen atom, a hydroxy or C_{1-3}-alkyl group:

By reacting a compound of general formula

$$R_a - A - Het - B - Ar - C(=NH) - Z_1 \quad , (II)$$

optionally formed in the reaction mixture,

wherein
A, B, Ar, Het and R_a are as hereinbefore defined and
Z_1 denotes an alkoxy or aralkoxy group such as the methoxy, ethoxy, n-propoxy, isopropoxy or benzyloxy group or an alkylthio or aralkylthio group such as the methylthio, ethylthio, n-propylthio or benzylthio group, with an amine of general formula

$$H_2N - R_b' \quad , (III)$$

wherein
R_b' denotes a hydrogen atom or a hydroxy or C_{1-3}-alkyl group.

The reaction is conveniently carried out in a solvent such as methanol, ethanol, n-propanol, water, methanol/water, tetrahydrofuran or dioxane at temperatures between 0 and 150°C, preferably at temperatures between 20 and 120°C, with a compound of general formula III or with a corresponding acid addition salt such as ammonium carbonate, for example.

A compound of general formula II may be obtained, for example, by reacting a compound of general formula I wherein E denotes a cyano group, with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzyl alcohol in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxane at temperatures between 0 and 50°C, but preferably at 20°C, or a corresponding nitrile with hydrogen sulphide, appropriately in a solvent such as pyridine or dimethylformamide and in the presence of a base such as triethylamine and subsequent alkylation of the resulting thioamide with a corresponding alkyl or aralkyl halide.

b. In order to prepare a compound of general formula I wherein the R_a-A- group and E are as hereinbefore defined, with the proviso that the R_a-A- group contains a carboxy group and E as hereinbefore defined or that the R_a-A- group is as hereinbefore defined and E denotes an NH_2-C(=NH)- group, or that the R_a-A- group contains a carboxy group and E denotes an NH_2-C(=NH)- group:

Converting a compound of general formula

$$R_a' - A - Het - B - Ar - C - E' \quad ,(IV)$$

wherein

A, B, Ar and Het are as hereinbefore defined and the R_a'-A- group and E' have the meanings given for the R_a-A- group and E hereinbefore, with the proviso that the R_a'-A- group contains a group which may be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and E is as hereinbefore defined or E' denotes a group which may be converted into an NH_2-C(=NH)- group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and the R_a'-A- group has the meanings given for the R_a-A- group hereinbefore or the R_a'-A- group contains a group which may be converted into a carboxyl group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis and E' denotes a group which may be converted into an NH_2-C(=NH)- group by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis,

is converted by hydrolysis, treatment with an acid or base, thermolysis or hydrogenolysis into a compound of general formula I, wherein the R_a-A- group and E are as hereinbefore defined, with the proviso that the R_a-A- group contains a carboxy group and E is as hereinbefore defined or the R_a-A- group has the meanings given above and E

denotes an NH_2-C(=NH)- group or the R_a-A- group contains a carboxy group and E denotes an NH_2-C(=NH)- group.

Examples of groups which may be converted into a carboxy group include a carboxyl group protected by a protecting group and the functional derivatives thereof, e.g. the unsubstituted or substituted amides, esters, thioesters, trimethylsilylesters, orthoesters or iminoesters which may conveniently be converted into a carboxyl group by hydrolysis,

the esters thereof with tertiary alcohols, e.g. the tert.butylester, which are conveniently converted into a carboxyl group by treatment with an acid or by thermolysis, and

the esters thereof with aralkanols, e.g. the benzylester, which are conveniently converted into a carboxyl group by hydrogenolysis.

The hydrolysis is expediently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between room temperature and the boiling temperature of the reaction mixture.

If the R_a'-A- group and/or E' in a compound of formula IV contains the tert.-butyl or tert.-butyloxycarbonyl group, for example, these may also be cleaved by treating with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid,

phosphoric acid or polyphosphoric acid, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane, preferably at temperatures between -10 and 120°C, e.g. at temperatures between 0 and 60°C, or thermally optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic quantity of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid, preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40 and 120°C.

If the R_a'-A- group and/or E' in a compound of formula IV contains the benzyloxy or benzyloxycarbonyl group, for example, these may also be cleaved by hydrogenolysis in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. at room temperature, under a hydrogen pressure of 1 to 5 bar.

c. In order to prepare a compound of general formula I wherein the R_a-A- group contains one of the ester groups mentioned in the definition of the R_a-A- group hereinbefore:

Reaction of a compound of general formula

$$R_a'' - A - Het - B - Ar - E \quad , (V)$$

wherein
B, E, Ar and Het are as hereinbefore defined and
the R_a"-A- group has the meanings given for the R_a-A- group hereinbefore, with the proviso that the R_a"-A- group

contains a carboxyl group or a group which may be converted into a corresponding ester group by means of an alcohol, with an alcohol of general formula

$$HO - R_7 \quad ,(VI)$$

wherein
R_7 is the alkyl moiety of one of the above-mentioned groups which may be cleaved *in vivo*, with the exception of the R_6-CO-O-(R_5CR_6)- group for a carboxyl group, or with the formamide acetals thereof.

or with a compound of general formula

$$Z_2 - R_8 \quad ,(VII)$$

wherein
R_8 denotes the alkyl moiety of one of the above-mentioned groups which may be cleaved *in vivo*, with the exception of the R_6-CO-O-(R_5CR_6)- group for a carboxyl group and
Z_2 denotes a leaving group such as a halogen atom, e.g. a chlorine or bromine atom.

The reaction with an alcohol of general formula VI is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, but preferably in an alcohol of general formula VI, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, thionyl chloride, trimethylchlorosilane, hydrochloric acid, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole, triphenylphosphine/carbon tetrachloride or triphenylphosphine/diethylazodicarboxylate, optionally

in the presence of a base such as potassium carbonate, N-ethyl-diisopropylamine or N,N-dimethylamino-pyridine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

With a compound of general formula VII the reaction is usefully carried out in a solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethylsulphoxide, dimethylformamide or acetone, optionally in the presence of a reaction accelerator such as sodium or potassium iodide and preferably in the presence of a base such as sodium carbonate or potassium carbonate or in the presence of a tertiary organic base such as N-ethyl-diisopropylamine or N-methyl-morpholine, which may act as solvent at the same time, or optionally in the presence of silver carbonate or silver oxide at temperatures between -30 and 100°C, but preferably at temperatures between -10 and 80°C.

d. In order to prepare a compound of general formula I wherein R_b denotes a group which may be cleaved *in vivo*:

Reacting a compound of general formula

$$R_a - A - Het - B - Ar - C(=NH) - NH_2 \quad ,(VIII)$$

wherein
R_a, A, Het, B and Ar are as hereinbefore defined, with a compound of general formula

$$Z_2 - R_5 \quad ,(IX)$$

wherein
R_5 denotes a group which may be cleaved *in vivo* and
Z_2 denotes a nucleofugic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom.

The reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or tertiary organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

With a compound of general formula IX, wherein Z_2 denotes a nucleofugic leaving group, the reaction is preferably carried out in a solvent such as methylene chloride, acetonitrile, tetrahydrofuran, toluene, dimethylformamide or dimethylsulphoxide, optionally in the presence of a base such as sodium hydride, potassium carbonate, potassium tert.-butoxide or N-ethyl-diisopropylamine at temperatures between 0 and 60°C.

e. In order to prepare a compound of general formula I wherein B denotes an ethylene group, in which a methylene group is replaced by a sulphinyl or sulphonyl group:

Oxidation of a compound of general formula

$$R_a - A - Het - B' - Ar - E \quad ,(X)$$

wherein
A, E, Ar, Het and R_a are as hereinbefore defined and
B' denotes an ethylene group, wherein a methylene group is replaced by a sulphenyl or sulphinyl group.

The oxidation is preferably carried out in a solvent or mixture of solvents, e.g. in water, water/pyridine, acetone, methylene chloride, glacial acetic acid, glacial acetic acid/acetic anhydride, dilute sulphuric acid or trifluoroacetic acid, and depending on the oxidising agent used, at temperatures between -80 and 100°C.

In order to prepare a corresponding sulphinyl compound of general formula I oxidation is conveniently carried out with one equivalent of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid, trifluoroacetic acid or formic acid at 0 to 20°C or in acetone at 0 to 60°C, with a peracid such as performic acid in glacial acetic acid or trifluoroacetic acid at 0 to 50°C or with m-chloroperbenzoic acid in methylene chloride, chloroform or dioxane at -20 to 80°C, with sodium metaperiodate in aqueous methanol or ethanol at -15 to 25°C, with bromine in glacial acetic acid or aqueous acetic acid, optionally in the presence of a weak base such as sodium acetate, with N-bromosuccinimide in ethanol, with tert.-butylhypochlorite in methanol at -80 to -30°C, with iodobenzodichloride in aqueous pyridine at 0 to 50°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid in glacial acetic acid or in acetone at 0 to 20°C and with sulphuryl chloride in methylene chloride at -70°C, the resulting thioether chlorine complex is conveniently hydrolysed with aqueous ethanol.

In order to prepare a sulphonyl compound of general formula I, oxidation is carried out starting from a corresponding sulphinyl compound, conveniently with one or more equivalents of the oxidising agent used, or starting from a corresponding sulphenyl compound, conveniently with two or more equivalents of the oxidising agent used, e.g. with hydrogen peroxide in glacial acetic acid/acetic anhydride, trifluoroacetic acid or in formic acid at 20 to 100°C or in acetone at 0 to 60°C, with a peracid such as performic acid or with m-chloroperbenzoic acid in glacial acetic acid, trifluoroacetic acid, methylene chloride or chloroform at temperatures between 0 and 60°C, with nitric acid in glacial acetic acid at 0 to 20°C, with chromic acid or

potassium permanganate in glacial acetic acid, water/sulphuric acid or in acetone at 0 to 20°C. Thus, by carrying out oxidation, for example, starting from a corresponding sulphenyl compound, preferably in methylene chloride, by treating with a corresponding amount of m-chloroperbenzoic acid at temperatures between 20°C and the reflux temperature of the reaction mixture, a corresonding sulphonyl compound of general formula I is obtained which may still contain a small amount of the corresponding sulphinyl compound.

f. In order to prepare a compound of general formula I wherein E is a cyano group and B is an ethylene group in which a methylene group linked either to group Het or to Ar is replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group:

Reacting a compound of general formula

$$R_a - A - Het - U \quad ,(XI)$$

with a compound of general formula

$$V - Ar - CN \quad ,(XII)$$

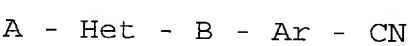
wherein
R_a, A, Ar and Het are as hereinbefore defined,
one of the groups U or V denotes an HO-, HS-, HOSO-, $HOSO_2-$ or HNR_1- group and the other group denotes a Z_3CH_2- group, wherein R_1 is as hereinbefore defined and Z_3 denotes a nucleofugic leaving group such as a halogen atom, e.g. a chlorine, bromine or iodine atom.

The reaction is preferably carried out in a solvent such as methanol, ethanol, methylene chloride, tetrahydrofuran, toluene, dioxane, dimethylsulphoxide or dimethylformamide, optionally in the presence of an inorganic or a tertiary

organic base, preferably at temperatures between 20°C and the boiling temperature of the solvent used.

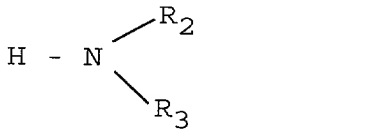
g. In order to prepare a compound of general formula I, wherein E is a cyano group and R_a denotes an R_2NR_3- group:

Reacting a compound of general formula



,(XIII)

wherein
A, B, Het and Ar are as hereinbefore defined, with an amine of general formula



,(XIV)

wherein
R_2 and R_3 are as hereinbefore defined, or with the reactive derivatives thereof.

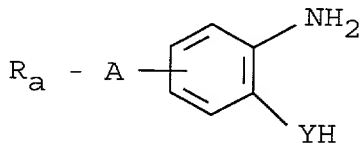
The reaction of an acid of general formula XIII is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or in a corresponding amine of general formula III, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl-chloroformate, tetraethylorthocarbonate, trimethylortho-acetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-

benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride and optionally with the addition of a base such as pyridine, 4-dimethylamino-pyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of a corresponding reactive compound of general formula XIII such as the esters, imidazolides or halides thereof with an amine of general formula XIV is preferably carried out in a corresponding amine as solvent, optionally in the presence of another solvent such as methylene chloride or ether and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

h. In order to prepare a benzimidazolyl, benzothiazolyl or benzoxazolyl compound of general formula I wherein B denotes an ethylene group:

Reacting a compound of general formula



, (XV)

wherein

R_a, A and Y are as hereinbefore defined, with a compound of general formula

$$HO\text{-}CO - CH_2CH_2 - Ar - E \qquad , (XVI)$$

wherein

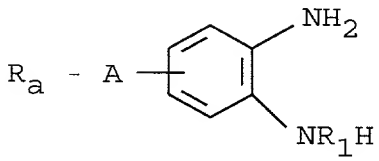
Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutylchloroformate, tetraethylorthocarbonate, trimethylorthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The reaction of a corresponding reactive compound of general formula XVI such as the esters, imidazolides or halides thereof with an amine of general formula XV is preferably carried out in a solvent such as methylene chloride, ether or tetrahydrofuran and preferably in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously be used as solvents, at temperatures between 0 and 150°C, preferably at temperatures between 50 and 100°C.

i. In order to prepare a quinoxalin-2-one compound of the general formula:

Reacting a compound of general formula



,(XVII)

wherein

R_a, R_1 and A are as hereinbefore defined, with a compound of general formula

$$HO\text{-}CO - COCH_2 - Ar - E \qquad ,(XVIII)$$

wherein

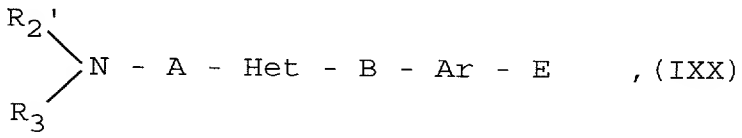
Ar and E are as hereinbefore defined, or with the reactive derivatives thereof.

The reaction is conveniently carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran, ethanol or dioxan, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, appropriately at temperatures of between 0 and 150°C, preferably at temperatures of between 0 and 100°C.

However, it is particularly preferred to carry out the reaction with a corresponding reactive compound of general formula XVIII such as the esters, imidazolides or halides thereof with an amine of general formula XVII in a solvent such as methylene chloride, ether, ethanol or tetrahydrofuran and optionally in the presence of a tertiary organic base such as triethylamine, N-ethyl-diisopropylamine or N-methyl-morpholine, which may simultaneously serve as solvent, at temperatures of between 0 and 150°C, preferably at temperatures of between 50 and 100°C.

j. In order to prepare a compound of general formula I wherein R_2 denotes a C_{1-4}-alkyl group substituted by an alkylsulphonylaminocarbonyl group:

Reacting a compound of general formula



, (IXX)

wherein

R_3, A, B, E, and Het are as hereinbefore defined and

R_2' denotes a C_{1-4}-alkyl group substituted by a carboxy group, or the reactive derivatives thereof, with a salt of a compound of general formula

$$C_{1-3}\text{-Alkyl-}SO_2\text{-}NH_2 \qquad (XX).$$

The reaction is preferably carried out with a corresponding reactive compound of general formula IXX such as the esters, imidazolides or halides thereof with a salt of a compound of general formula XX, preferably with an alkali metal salt thereof such as a sodium salt, in a solvent such as methylene chloride, ether, ethanol, tetrahydrofuran or

dimethylformamide at temperatures between 0 and 150°C, preferably at temperatures of between 50 and 100°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by means of conventional protecting groups which are removed by cleaving after the reaction.

For example, the protecting group for a hydroxy group may be the trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

the protecting group for a carboxyl group may be the trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group, and

the protecting group for an amino, alkylamino or imino group may be the acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and for the amino group the phthalyl group may also be considered.

The optional subsequent cleaving of a protecting group may, for example, be carried out hydrolytically in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether cleaving, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group may for example be cleaved hydrogenolytically, e.g. using hydrogen in the presence of a catalyst such as

palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid, at temperatures between 0 and 50°C, but preferably at room temperature, under a hydrogen pressure of 1 to 7 bar, preferably 3 to 5 bar.

A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures between 0 and 50°C, but preferably at room temperature.

However, a 2,4-dimethoxybenzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treatment with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane, or ether.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane, at temperatures between 20 and 50°C.

An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-palladium(0), preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone, at temperatures between 0 and 100°C, preferably at room temperature and under inert gas, or by treating with a catalytic amount of tris-(triphenylphosphine)-rhodium(I)-chloride, in a solvent such as aqueous ethanol and optionally in the presence of a base such as 1,4-

diazabicyclo[2.2.2]octane, at temperatures between 20 and 70°C.

The compounds of general formulae II to XX used as starting materials, some of which are known from the literature, may be obtained by methods known from the literature and moreover their production is described in the Examples.

Thus, for example, a compound of general formula II is obtained by reacting a corresponding nitrile which in turn is conveniently obtained by processes f to h, with a corresponding thio or alcohol in the presence of hydrogen chloride or bromide.

A compound of general formulae IV, V, VIII, X and IXX used as starting material is conveniently obtained according to a process of the present invention.

A starting compound of general formula XI in which U denotes a halomethyl group is conveniently obtained by cyclisation of a corresponding ester which is substituted in the o-position by a suitable halogen atom and a methoxyacetamido group, to form a corresponding bicyclic 2-alkoxymethyl compound, optionally subsequent hydrolysis and optionally subsequent amidation of a resulting carboxylic acid with a corresponding amine, converting the alkoxymethyl compound thus obtained into the corresponding halomethyl compound, which can if necessary be subsequently converted into the desired compound by means of a suitable compound. If the cyclisation is carried out with a suitable carbonic acid derivative, a starting compound of general formula XI is obtained wherein U denotes a hydroxy, mercapto or amino group.

A starting compound of general formula XIII is obtained by cyclisation of a corresponding o-disubstituted ester, followed by saponification of the resulting ester and

subsequent amidation of the carboxylic acid thus obtained with a corresponding amine.

Furthermore, an imidazopyridine substituted in the 5-position by a methyl group and obtained by cyclisation can be converted, via the corresponding N-oxide, into the corresponding hydroxymethyl compound which is converted by oxidation into the desired carboxylic acid of general formula XIII.

The compounds of general formulae III, VI, VII, IX and XII used as starting materials are obtained by conventional methods, for example by reducing an aromatic ester substituted in the o-position by an optionally substituted amino group and a nitro group, and optionally subsequent cyclisation of the resulting o-diamino compound with a corresponding carboxylic acid.

Furthermore, the compounds of general formula I obtained may be separated into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur in racemate form may be separated by methods known *per se* (see Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes, and compounds of general formula I having at least 2 asymmetric carbon atoms may be separated on the basis of their physical-chemical differences using known methods, e.g. by chromatography and/or fractional crystallisation, into the diastereomers thereof, which, if they occur in racemic form, may subsequently be separated into the enantiomers as mentioned above.

The separation of enantiomers is preferably effected by column separation on chiral phases or by recrystallisation

from an optically active solvent or by reacting with an optically active substance, especially acids and the activated derivatives thereof or alcohols, which forms salts or derivatives such as e.g. esters or amides with the racemic compound, and separation of the diastereomeric salt mixture or derivative thus obtained, e.g. on the basis of their different solubilities, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Particularly common, optically active acids are, for example, the D- and L-forms of tartaric acid, and dibenzoyltartaric acid, di-o-tolyl tartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid and quinaldic acid. Examples of optically active alcohols include for example (+)- or (-)-menthol and examples of optically active acyl groups in amides include, for example, (+)- or (-)-menthyloxycarbonyl.

Moreover, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of suitable acids include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

In addition, the new compounds of formula I thus obtained, if they contain a carboxyl group, may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof. Examples of suitable bases include for example sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As already mentioned, the new compounds of general formula I and the salts thereof have valuable properties. Thus, the compounds of general formula I wherein E denotes a cyano group are valuable intermediate products for preparing the other compounds of general formula I and the compounds of general formula I wherein E denotes an $R_bNH-C(=NH)-$ group and the tautomers, the stereoisomers and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly a thrombin-inhibiting effect, an effect of prolonging the thrombin time and an inhibitory effect on related serine proteases such as e.g. trypsin, urokinase factor VIIa, factor Xa, factor IX, factor XI and factor XII, whilst a few compounds such as for example the compound of Example 16 simultaneously also have a slight inhibitory effect on thrombocyte aggregation.

For example, the following compounds:

A = 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,

B = 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonyl-propyl)-amide,

C = 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid -N-phenyl-N-(hydroxycarbonyl-methyl)-amide,

D = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

E = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,

F = 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and

G = 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

were investigated as follows for their effects on thrombin time:

Materials: plasma, from human citrated blood.
Test thrombin (bovine), 30U/ml, Behring Werke, Marburg
Diethylbarbiturate acetate buffer, ORWH 60/61, Behring Werke, Marburg
Biomatic B10 coagulometer, Sarstedt

Method:

The thrombin time was determined using a Biomatic B10 coagulometer made by Messrs. Sarstedt.

As the test substance, 0.1 ml of human citrated plasma and 0.1 ml diethylbarbiturate buffer (DBA buffer) were added to the test strip prescribed by the manufacturer. The mixture was incubated for one minute at 37°C. The clotting reaction was started by the addition of 0.3 U test thrombin in 0.1 ml DBA buffer. The time is measured using the apparatus from the addition of the thrombin up to the clotting of the mixture. Mixtures to which 0.1 ml of DBA buffer were added were used as the controls.

According to the definition, a dosage-activity curve was used to determine the effective concentration of the

substance, i.e. the concentration at which the thrombin time is double compared with the control.

The Table which follows contains the results found:

Substance	Thrombin time (ED_{200} in μM)
A	0.04
B	0.06
C	0.15
D	0.03
E	0.09
F	0.03
G	0.03

By way of example, no acute toxic side effects were observed when compounds A, D, E and G were administered to rats in doses of up to 10 mg/kg i.v. The compounds are thus well tolerated.

In view of their pharmacological properties the new compounds and the physiologically acceptable salts thereof are suitable for the prevention and treatment of venous and arterial thrombotic diseases, such as for example the treatment of deep leg vein thrombosis, for preventing reocclusions after bypass operations or angioplasty (PT(C)A), and occlusion in peripheral arterial diseases such as pulmonary embolism, disseminated intravascular coagulation, for preventing coronary thrombosis, stroke and the occlusion of shunts or stents. In addition, the compounds according to the invention are suitable for antithrombotic support in thrombolytic treatment, such as for example with rt-PA or streptokinase, for preventing long-term restenosis after PT(C)A, for preventing metastasis and the growth of clot-dependent tumours and fibrin-dependent inflammatory processes.

The dosage required to achieve such an effect is appropriately 0.1 to 30 mg/kg, preferably 0.3 to 10 mg/kg by intravenous route, and 0.1 to 50 mg/kg, preferably 0.3 to 30 mg/kg by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention:

Preliminary remarks

Unless otherwise specified, the R_f values were always determined using polygram silica gel plates produced by Messrs. E. Merck of Darmstadt.

The EKA mass spectra (electrospray mass spectra of cations) are described, for example, in "Chemie unserer Zeit 6, 308-316 (1991).

Example 1

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid -N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

a) Methyl 6-methylamino-5-nitro-nicotinate

1.6 g (7.4 mMol) of methyl 6-chloro-5-nitro-nicotinate (see Bernie et al. in J. Chem. Soc. 1951, 2590) were stirred in 20 ml of 40% aqueous methylamine solution at room temperature for 30 minutes. The reaction mixture was then diluted with ice water, the yellow precipitate formed was filtered off and dried.

Yield: 1.2 g (80 % of theory),

R_f value: 0.66 (silica gel; ethyl acetate/ethanol/glacial acetic acid = 90:5:5)

b) Methyl 5-amino-6-methylamino-nicotinate

To a solution of 3.1 g (15 mMol) of methyl 6-methylamino-5-nitro-nicotinate in 100 ml of ethanol/dichloromethane (3:1) was added 1 g of palladium on charcoal (10%) and the resulting suspension was hydrogenated at room temperature under 5 bar of hydrogen pressure for 1.5 hours. The catalyst was then filtered off and the solvent was distilled off *in vacuo*. The crude oily product obtained was further reacted directly.

Yield: 2.4 g (92 % of theory),

R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

c) Methyl 5-[2-(4-cyanophenyl)ethylcarbonylamino]-6-methylamino-nicotinate

A solution of 2.6 g (15 mMol) of 3-(4-cyanophenyl)propionic acid in 25 ml of absolute tetrahydrofuran was mixed with 2.4 g (15 mMol) of N,N'-carbonyldiimidazole and stirred for 20 minutes at room temperature. Then the imidazolide was mixed with a solution of 2.3 g (13 mMol) of methyl 5-amino-6-methylamino-nicotinate in 25 ml of dimethylformamide and heated for 3 hours to 100°C. After the removal of the solvent *in vacuo* the crude product obtained was taken up in ethyl acetate, the organic phase was washed with water and after drying over sodium sulphate it was again freed from solvent. The residue obtained was purified by flash chromatography (silica gel; gradient: dichloromethane to dichloromethane/ethanol = 19:1).

Yield: 2.1 g (50 % of theory) of beige solid

R_f value: 0.54 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

d) Methylyl 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylate

A solution of 2.0 g (5.9 mMol)of methyl 5-[2-(4-cyanophenyl)ethylcarbonylamino]-6-methylamino-nicotinate in 50 ml glacial acetic acid was heated to 100°C for one hour. After removal of the solvent the residue was taken up in dichloromethane, washed with sodium hydrogen carbonate solution, dried with sodium sulphate and the solvent was distilled off again.

Yield: 1.7 g brown solid (89 % of theory),

R_f value: 0.50 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

e) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid

A solution of 3.2 g (10 mMol) of methyl 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4.5-b]pyridine-6-carboxylate in 150 ml methanol was mixed with a solution of 1.5 g lithium hydroxide in 20 ml water and stirred for 24 hours at room temperature. Then the mixture was diluted with 50 ml of water, the alcohol was distilled off and the aqueous phase was washed with ethyl acetate. After acidification with dilute hydrochloric acid the mixture was extracted several times with dichloromethane/methanol (9:1), the organic phase was dried with sodium sulphate and the solvent was distilled off.

Yield: 2.1 g beige solid (70 % of theory),

R_f value: 0.38 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

f) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonyl-ethyl)-amide

A solution of 2.0 g (6.5 mMol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid in 100 ml dichloromethane was mixed with 20 ml thionyl chloride and refluxed for 2 hours. After the liquid components had been distilled off the crude product was taken up twice more in dichloromethane and the solvent was distilled off each time. The crude acid chloride thus obtained (2 g) was suspended in 100 ml of tetrahydrofuran and mixed with 1.2 g (6.5 mMol) of N-(2-ethoxycarbonyl-ethyl)aniline. Then within 5 minutes 0.73 g (7.2 mMol) of triethylamine were added dropwise. After 1 hour's stirring the solvent was distilled off *in vacuo*, the residue was taken up in ethyl acetate, the organic phase was washed with water and dried with sodium sulphate. After distillation of the solvent and flash chromatography (silica gel; dichloromethane to dichloromethane/ethanol = 49:1) the desired compound was isolated as a brownish oil.

Yield: 1.9 g (65 % of theory),
R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

g) 3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

1.8 g (3.7 mMol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred into 100 l of ethanol saturated with hydrogen chloride for 16 hours first at 0°C and then at room temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off, the oily residue was taken up in 50 ml of absolute ethanol and mixed with 3.6 g (37 mMol) of ammonium carbonate. After 4 hours the solvent was distilled off *in vacuo*, the crude product obtained was purified by flash chromatography (silica gel; gradient: dichloromethane/ethanol 19:1 to 4:1) and evaporated down again.
Yield: 1.6 g of beige solid (80 % of theory),
R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia = 90:5:5)

Example 2

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]-pyridine-6-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

A solution of 535 mg (1.0 mMol) of 3-methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridine-6-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide in 10 ml ethanol was mixed with 5 ml of 2N sodium hydroxide solution and stirred for 2 hours at room temperature. Then the mixture was diluted with 10 ml water, the alcohol was distilled off, the aqueous phase was washed with 20 ml

ethyl acetate and acidified with concentrated hydrochloric acid, whereupon the desired compound was precipitated in the form of white crystals.

Yield: 375 mg (74 % of theory),

R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 90:5:5)

$C_{26}H_{26}N_6O_3$ (470.54)

Mass spectrum: $(M+H)^+$ = 471

Example 3

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide, methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 75 % of theory,

$C_{26}H_{27}N_7O_3$ (485.55)

R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 486

Example 4

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-ethoxycarbonylmethyl-amide-hydrochloride

---

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-ethoxycarbonylmethyl-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 84 % of theory,

$C_{27}H_{28}N_6O_3$ (484.56)

R_f value: 0.44 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+ = 485$

Example 5

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-hydroxycarbonylmethyl-amide-hydrochloride

---

Prepared analogously to Example 2 from 3-methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-ethoxycarbonylmethyl-amide-hydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{25}H_{24}N_6O_3$ (456.51)

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+ = 457$

Example 6

2-[2-(4-amidinophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-hydrochloride

---

Prepared analogously to Example 1 from 2-[2-(4-cyanophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine, methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 20 % of theory,

$C_{27}H_{26}N_6O_3$ (482.54)

R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia

= 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 483

Example 7

2-[2-(4-amidinophenyl)ethyl]-3-methyl-6-(2-carboxy-2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-hydrochloride

---

Prepared analogously to Example 2 from 2-[2-(4-amidinophenyl)ethyl]-3-methyl-6-(2-methoxycarbonyl-2,3-dihydroindol-1-yl-carbonyl)-imidazo[4,5-b]pyridine-hydrochloride and sodium hydroxide solution.
Yield: 90 % of theory,
$C_{26}H_{24}N_6O_3$ (468.52)
R_f value: 0.24 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)
EKA mass spectrum: $(M+H)^+$ = 469
$(M+Na)^+$ = 491

Example 8

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

a) 2-Amino-3-methylamino-6-methyl-pyridine

8.35 g (50 mMol) of 2-Methyl-5-methylamino-6-nitro-pyridine (Heterocycles 38, 529 (1994)) were dissolved in 300 l ethyl acetate and hydrogenated with 1.5 g Raney nickel for 3.5 hours at room temperature. Then the catalyst was filtered off and the filtrate was evaporated down. After crystallisation of the resulting residue from petroleum ether, 5.75 g (84 % of theory) were obtained as olive-green crystals.
$C_7H_{11}N_3$ (137.20)

Melting point: 112-113°C

b) 1,5-Dimethyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]-pyridine

11.4 g (63 mMol) of 4-cyano-phenoxyacetic acid were dissolved in 200 ml of absolute tetrahydrofuran and mixed at room temperature with 10.2 g (63 mMol) of N,N'-carbonyldiimidazole. After 15 minutes at 60°C, 5.70 g (41.5 mMol) of 2-amino-3-methylamino-6-methyl-pyridine were added. After 2 hours at 60°C the solvent was distilled off and the crystalline residue was mixed with water, washed with water and dried. After crystallisation from ethanol 9.95 g (91 % of theory) were obtained in the form of white crystals.

$C_{16}H_{14}N_4O$ (278.32)

Mass spectrum: $M^+ = 278$

c) 1,5-Dimethyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-4-N-oxide

2.62 g (10 mMol) of 1,5-dimethyl-2-[(4-cyanophenyl)-oxymethyl]-imidazo[4,5-b]pyridine were suspended in 125 ml dichloromethane and mixed with 2.62 g (12.7 mMol) of m-chloroperbenzoic acid, whereupon a clear solution was obtained. After 2 hours at room temperature the solvent was distilled off and the residue obtained was mixed with a sodium hydrogen carbonate solution. After 30 minutes the white crystalline product obtained was suction filtered, washed with water and dried at 40°C.

Yield: 2.45 g (83 % of theory),

$C_{16}H_{14}N_4O_2$ (294.30)

Mass spectrum: $M^+ = 294$

d) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-5-hydroxymethyl-imidazo[4,5-b]pyridine

2.40 g (8.2 mMol) of 1,5-dimethyl-2-[(4-cyanophenyl)-oxymethyl]-imidazo[4,5-b]pyridin-4-N-oxide were suspended in 75 ml dichloromethane and mixed with 2.4 ml of

trifluoroacetic acid anhydride (16.9 mMol), whereupon a clear solution was obtained. After 16 hours at room temperature the solvent was distilled off, the viscous residue obtained was taken up in 50 ml dichloromethane and covered with 50 ml of 2M sodium hydrogen carbonate solution. After 3 hours' vigorous stirring the precipitate formed was suction filtered, washed with water and dried at 40°C.

Yield: 1.85 g white powder (78 % of theory),

$C_{16}H_{14}N_4O_2$ (294.30)

Melting point: 172°C

e) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]-pyridine-5-carbaldehyde

3.65 g (12.5 mMol) of 1-methyl-2-[(4-cyanophenyl)-oxymethyl]-5-hydroxymethyl-imidazo[4,5-b]pyridine were dissolved in 500 ml dichloromethane and mixed with 15.0 g of manganese dioxide. After 96 hours at room temperature the mixture was filtered through kieselgur and the solvent was distilled off. The filtrate obtained was evaporated down, the crystalline precipitate was triturated with ether, suction filtered and dried.

Yield: 3.05 g white powder (84 % of theory),

$C_{16}H_{12}N_4O_2$ (292.30)

Melting point: 231-234°C

f) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-5-carboxy-imidazo-[4.5-b]pyridine

1.25 g (4.3 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridine-5-carbaldehyde were dissolved in 10 ml formic acid and mixed at 0°C with 1.0 ml hydrogen peroxide (33% strength). After 12 hours at 4°C the white precipitate formed was suction filtered, washed with water and dried at 40°C.

Yield: 0.81 g (61 % of theory),

$C_{16}H_{12}N_4O_3$ (308.7)

g) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

308 mg (1.0 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-5-carboxy-imidazo[4.5-b]pyridine were suspended in 5 ml of dimethylformamide and mixed with 303 mg (3.0 mMol) of N-methyl-morpholine and 321 mg (1.0 mMol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate. After 10 minutes at room temperature a solution of 215 mg (1.2 mMol) of methyl N-(2-pyridyl)-3-amino-propionate in 2 ml of dimethylformamide was added, whereupon a clear solution was obtained. After 12 hours at room temperature the reaction solution was stirred into ice-water. After extracting 3 times with ethyl acetate the combined organic extracts were washed with a saline solution, dried over sodium sulphate and evaporated down. The residue obtained was chromatographed on silica gel with dichloromethane/ethanol (90:1 to 25:1).

Yield: 165 mg of white powder (35 % of theory),

$C_{25}H_{12}N_6O_4$ (407.50)

Melting point: 139-140°C

h) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-imidazo[4.5-b]-pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl-ethyl)-amide

Prepared by reacting 140 mg (0.3 mMol) of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-imidazo[4,5-b]pyridin-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide with ethanol saturated by hydrogen chloride and with ammonium carbonate/ethanol analogously to Example 1g. The resulting product was purified by chromatography over silica gel with dichloromethane/ethanol (19:1 to 4:1).

Yield: 48 mg of white powder (36 % of theory),

$C_{26}H_{27}N_7O_4$ (501.57)

Mass spectrum: $(M+H)^+ = 502$

Example 9

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

a) Ethyl 4-fluoro-3-methoxyacetamido-benzoate

A solution of 2.8 g (15.3 mMol) of ethyl 3-amino-4-fluoro-benzoate (cf. L.S. Fosdick, A.F. Dodds in J. Amer. Chem. Soc. 65, 2305 (1943)) and 1.56 ml (1.85 g = 17.0 mMol) of methoxyacetylchloride in 50 ml chlorobenzene was stirred for 1 hour at 50°C and then refluxed for 15 minutes. Then the solvent was distilled off *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; dichloromethane/ethanol = 100:1). The desired compound, initially oily, solidified within a few days.
Yield: 3.8 g (98 % of theory),
R_f value: 0.38 (silica gel; dichloromethane/ethanol = 19:1)

b) Ethyl-2-methoxymethyl-benzothiazole-5-carboxylate

A mixture of 3.0 g (11.7 mMol) of 4-fluoro-3-methoxyacetamido-benzoic acid and 2.1 g (5.2 mMol) of Lawesson's reagent was refluxed for 6 hours in 90 ml toluene, mixed with 1.0 g Lawesson's reagent and heated to 120°C for another 6 hours. After the solvent was replaced with xylene the mixture was heated to 180°C for a further 8 hours in a pressurised vessel. Then the solvent was distilled off *in vacuo*, the crude product obtained was purified by flash chromatography (silica gel; ethyl acetate/petroleum ether = 5:95) and evaporated down again.
Yield: 2.1 g of yellow crystals (72 % of theory),
R_f value: 0.55 (silica gel; ethyl acetate/petroleum ether = 3:7)

c) 2-Methoxymethyl-benzothiazole-5-carboxylic acid

A mixture of 2.1 g (8.36 mMol) of ethyl 2-methoxymethyl-benzothiazole-5-carboxylate and 16 ml of 2N sodium hydroxide solution was stirred into 60 ml ethanol for 1

hour at room temperature. Then the alcohol was distilled off, the crude product was taken up in 20 ml water, washed with 50 ml diethylether and the aqueous phase was acidified with concentrated hydrochloric acid whilst being cooled with ice. The pinkish-beige compound thereby precipitated was suction filtered, washed with water and dried.
Yield: 1.6 g (86 % of theory),
R_f value: 0.12 (silica gel; dichloromethane/ethanol = 29:1)

d) 2-Methoxymethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide
A suspension of 1.6 g (7.2 mMol) of 2-methoxymethyl-benzothiazole-5-carboxylic acid in 60 ml dichloromethane was mixed with 1.6 ml (22 mMol) of thionyl chloride and refluxed for 1 hour. The solid dissolved after 20 minutes. After distillation of the liquid components the crude product was taken up in dichloromethane twice more and each time the solvent was distilled off. The crude acid chloride thus obtained was taken up in 50 ml of tetrahydrofuran, added dropwise to a mixture of 1.4 g (7.2 mMol) of N-(2-ethoxycarbonylethyl)aniline and 3.0 ml (21 mMol) of triethylamine in 50 ml of tetrahydrofuran and stirred overnight at room temperature. Then the solvent was distilled off *in vacuo*, the residue was taken up in 30 ml of dichloromethane, this solution was washed with water and dried with sodium sulphate. After distillation of the solvent and flash chromatography (silica gel; gradient: dichloromethane/ethanol 98.5:1.5 to 80:20) the desired compound was isolated as a brownish oil.
Yield: 2.05 (72 % of theory),
R_f value: 0.40 (silica gel; ethyl acetate/petroleum ether = 1:1)

e) 2-[N-(4-Cyanophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide
A mixture of 2.05 g (5.14 mMol) of 2-methoxymethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-

ethoxycarbonylethyl)-amide and 5.7 ml (5.7 mMol) of a 1M solution of boron tribromide in dichloromethane was dissolved in a further 60 ml of dichloromethane and stirred for 16 hours at room temperature. Then the mixture was washed with 40 ml of saturated sodium hydrogen carbonate solution, the organic phase was dried with sodium sulphate and the solvent was distilled off. The crude 2-bromomethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide thus obtained (2.4 g) was taken up in 5.0 ml of N,N-diisopropyl-ethylamine and mixed with 0.64 g (5.4 mMol) of 4-amino-benzonitrile. After 1 hour's heating to 130°C the solvent was distilled off *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; gradient: ethyl acetate/petroleum ether = 1:3 to 1:1), whilst an orange foam was obtained when the eluates were evaporated down.
Yield: 1.1 g (44 % of theory),
R_f value: 0.35 (silica gel; ethyl acetate/petroleum ether = 7:3)

f) <u>2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide</u>

1.1 g (2.27 mMol) of 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide was stirred in 100 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C and then at room temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C and the oily residue was taken up in 100 ml of absolute ethanol and mixed with 1.6 g (22 mMol) of ammonium carbonate. After 18 hours stirring at room temperature the solvent was distilled off *in vacuo* and the crude product was purified by flash chromatography (silica gel; gradient: water/methanol = 19:1 to 4:1). When the eluates are evaporated down the desired compound is obtained as a white foam.

Yield: 0.77 g (63 % of theory),
R_f value: 0.19 (silica gel; dichloromethane/ethanol = 3:7)
$C_{27}H_{27}N_5O_3S$ (501.60)
Mass spectrum: $(M+H)^+ = 502$

Example 10

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide

---

0.45 g (0.84 mMol) of 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were dissolved in 15 ml of ethanol, mixed with 2 ml of 2N sodium hydroxide solution and stirred for 4 hours at room temperature. Then the mixture was acidified with 3 ml of 2N hydrochloric acid and the solvent was distilled off. The crude product obtained was taken up in 5 ml dichloromethane/ethanol (2:1) and filtered to remove the insoluble sodium chloride. After the distillation of the solvent the desired compound was obtained as a yellow foam.
Yield: 0.26 g (67 % of theory),
R_f value: 0.47 (silica gel; methanol/5 % aqueous sodium chloride = 6:4)
$C_{25}H_{23}N_5O_3S$ (473.55)
Mass spectrum: $(M+H)^+ = 474$

Example 11

2-[N-(4-amidinophenyl)-aminomethyl]benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-dihydrochloride

---

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide, methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 68 % of theory,

$C_{25}H_{24}N_6O_3S$ (488.57)

R_f value: 0.13 (silica gel; methylene chloride/ethanol = 4:1 +a few drops of acetic acid)

EKA mass spectrum : $(M+H)^+ = 489$

Example 12

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 9 from 2-[2-(4-cyanophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 95 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.20 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 488$

Example 13

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 68 % of theory,

$C_{25}H_{24}N_6O_3S$ (488.57)

R_f value: 0.14 (silica gel; methylene chloride/ethanol =

4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 489

Example 14

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution.
Yield: 90 % of theory,
$C_{23}H_{20}N_6O_3S$ (460.52)
R_f value:
EKA mass spectrum: $(M+H)^+$ = 461
$(M+Na)^+$ = 483
$(M+2Na)^{++}$ = 253

Example 15

2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 2-[N-(4-Cyanophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 9e from 4-cyano-N-methyl-aniline and 2-methoxymethyl-benzothiazole-5-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide.
Yield: 57 % of theory,
R_f value: 0.46 (silica gel; dichloromethane/ethanol = 19:1).

b) 2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 73 % of theory,

$C_{28}H_{29}N_5O_3S$ (515.64)

R_f value:0.29 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 516$

Example 16

2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 96 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.48 (Merck RP-8, methanol/5% NaCl solution = 6:4)

EKA mass spectrum: $(M+H)^+ = 488$

$(M+2Na)^{++} = 266.5$

Example 17

2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 9 from 2-[(4-cyanophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 61 % of theory,
$C_{27}H_{26}N_4O_3S_2$ (518.66)
R_f value: 0.27 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)
EKA mass spectrum: $(M+H)^+$ = 519

Example 18

2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 2-[(4-amidinophenyl)thio-methyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 95 % of theory,
$C_{25}H_{22}N_4O_3S_2$ (490.61)
R_f value: 0.25 (Merck RP-8, methanol/5% NaCl solution = 6:4)
EKA mass spectrum: $(M+H)^+$ = 491
$(M+Na)^+$ = 513

Example 19

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 82 % of theory,
$C_{26}H_{25}N_5O_3S$ (487.58)
R_f value: 0.21 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)
EKA mass spectrum: $(M+H)^+ = 488$

Example 20

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 75 % of theory,
$C_{24}H_{21}N_5O_3S$ (459.53)
R_f value: 0.14 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)
EKA mass spectrum: $(M+H)^+ = 460$
$(M+Na)^+ = 482$

Example 21

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 9 from 2-[2-(4-cyanophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 80 % of theory,

$C_{28}H_{28}N_4O_3S$ (500.62)

R_f value: 0.30 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 501

Example 22

2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 2-[2-(4-amidinophenyl)ethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 77 % of theory,

$C_{26}H_{24}N_4O_3S$ (472.57)

R_f value: 0.18 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 473

$(M+Na)^+$ = 495

$(M+H+Na)^{++}$ = 259

Example 23

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 9 from 2-[N-(4-cyanophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 83 % of theory,

$C_{24}H_{29}N_5O_3$ (467.59)

R_f value: 0.31 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 468

$(2M+H)^+$ = 935

Example 24

2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 2-[N-(4-amidinophenyl)-aminomethyl]-benzothiazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 75 % of theory,

$C_{22}H_{25}N_5O_3S$ (439.54)

R_f value: 0.14 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 440

$(M+H+Na)^{++}$ = 231.6

Example 25

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 4-Methylamino-3-nitro-benzoic acid-N-phenyl-N-(2-ethoxy-carbonylethyl)-amide

To a solution of 24.7 g (0.115 mol) of 4-methylamino-3-nitro-benzoic acid chloride and 22.3 g (0.115 mol) of N-(2-ethoxy-carbonylethyl)-aniline in 300 ml of tetrahydrofuran, 13.1 g (0.13 mol) of triethylamine were added dropwise in 15 minutes, with stirring, at room temperature. After 2 hours stirring the solvent was distilled off in a water-jet vacuum and the residue was mixed with 700 ml of water with stirring. The mixture was extracted 3 times with 200 ml of dichloromethane, the organic extract was washed twice with 200 ml of 2N hydrochloric acid and twice with 300 ml of water and dried over sodium sulphate. The solvent was then distilled off and the oily product thus obtained was purified by column chromatography (1 kg silica gel; eluant: petroleum ether/ethyl acetate = 2:1).

Yield: 35.0 g (82 % of theory),

R_f value: 0.28 (silica gel; dichloromethane/ethanol = 50:1)

b) 3-Amino-4-methylamino-benzoic acid-N-phenyl-N-(2-ethoxy-carbonylethyl)-amide

12.1 g (0.0326 mol) of 4-methylamino-3-nitro-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were hydrogenated in 300 ml ethanol and 150 ml dichloromethane after the addition of about 4 g of palladium/charcoal (10%) at room temperature and under a hydrogen pressure of 5 bar. Then the catalyst was filtered off and the filtrate was evaporated down. The crude product thus obtained was reacted without further purification.

Yield: 10.6 g (95 % of theory),
R_f value: 0.19 (silica gel; dichloromethane/ethanol = 50:1)

c) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

6.17 g (0.035 mol) of N-(4-cyanophenyl)glycine and 5.68 g (0.035 mol) of N,N'-carbonyldiimidazole were refluxed in 300 ml of tetrahydrofuran for 30 minutes, then 10.6 g (0.032 mol) of 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were added and the mixture was refluxed for a further five hours. Then the solvent was distilled off *in vacuo*, the residue was dissolved in 150 ml of glacial acetic acid and refluxed for one hour. Then the glacial acetic acid was distilled off *in vacuo*, the residue was dissolved in about 300 ml of dichloromethane, the solution was washed twice with about 150 ml water and then dried over sodium sulphate. After evaporation of the solvent the crude product thus obtained was purified by column chromatography (800 g silica gel; eluant: dichloromethane with 1-2 % ethanol).
Yield: 8.5 g (57 % of theory),
R_f value: 0.51 (silica gel; dichloromethane/ethanol = 19:1)

d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.2 g (2.49 mMol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 100 ml of saturated ethanolic hydrochloric acid for 6 hours at room temperature. Then the mixture was evaporated to dryness *in vacuo*, the residue was dissolved in 100 ml of ethanol, mixed with 2.5 g (26 mMol) of ammonium carbonate and stirred overnight at room temperature. After distillation of the solvent the crude product thus obtained was purified by column chromatography (100 g silica gel; eluant:

dichloromethane/ethanol = 4:1). By concentrating the eluates the desired compound was obtained as a white, amorphous solid.

Yield: 1.10 g (83 % of theory),

R_f value: 0.18 (silica gel; dichloromethane/ethanol = 4:1)

$C_{28}H_{30}N_6O_3$ x HCl (498.6)

EKA mass spectrum: $(M+H)^+$ = 499

$(M+2H)^{++}$ = 250

$(M+H+Na)^{++}$ = 261

Example 26

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

A mixture of 300 mg (0.56 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride, 15 ml of ethanol, 4 ml of water and 120 mg (3.0 mMol) of sodium hydroxide was stirred for two hours at room temperature. Then the mixture was diluted with about 20 ml of water and made weakly alkaline with glacial acetic acid. The product which crystallised out was suction filtered, washed with water and dried at 60°C *in vacuo*.

Yield: 250 mg (95 % of theory),

$C_{26}H_{26}N_6O_3$ (470.5)

EKA mass spectrum: $(M+H)^+$ = 471

$(M+H+Na)^{++}$ = 247

$(M+2Na)^{++}$ = 258

Example 27

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 4-Methylamino-3-chloracetamido-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

A solution of 1.8 g (5.9 mMol) of 3-amino-4-methylamino-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide [prepared analogously to 3-amino-4-ethylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide], 1.1g (6.8 mMol) of N,N'-carbonyldiimidazole and 0.65 g (6.9 mMol) of chloroacetic acid in 75 ml tetrahydrofuran was stirred for 1 hour at room temperature. Then the solvent was distilled off *in vacuo*, and the crude product was purified by flash chromatography (silica gel; methylene chloride/ethanol = 49:1).

Yield: 1.7 g (77% of theory) yellow oil,

R_f value: 0.58 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

b) 2-Chloromethyl-1-methyl-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

1.6 g (4.3 mMol) of 4-methylamino-3-chloracetamido-benzoic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide were heated to 100°C in 25 ml of acetic acid for 30 minutes. Then the solvent was distilled off, the crude product was taken up in 40 ml methylene chloride/ethanol (9:1) and washed with 20 ml saturated sodium hydrogen carbonate solution. The organic phase was dried with sodium sulphate and evaporated down.

Yield: 1.5 g (100% of theory) of brown oil,

R_f value: 0.63 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

c) 1-Methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide

A mixture of 1.5 g (4.1 mMol) of 2-chloromethyl-1-methyl-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide and 0.65 g (4.8 mMol) of p-cyanothiophenol was heated in 10 ml of dimethylformamide and 10 ml of diisopropylethylamine for 1 hour to 100°C. The solvent was distilled off *in vacuo*, the crude product was dissolved in 30 ml ethyl acetate, washed with 30 ml water, and after concentration purified by flash chromatography (silica gel; methylene chloride/ethanol (49:1 to 19:1).

Yield: 1.5 g (79% of theory) of brown oil,

R_f value: 0.65 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

d) 1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.4 g (3.01 mMol) of 1-methyl-2-[(4-cyanophenyl)-thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide were stirred in 50 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C, later at room temperature, until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue was taken up in 40 ml of absolute ethanol and mixed with 2.8 g of ammonium carbonate. After 18 hours the solvent was distilled off *in vacuo* and the crude product was purified by flash chromatography (silica gel; methylene chloride/ethanol = 19:1 to 4:1).

Yield: 1.3 g (83% of theory) as a light beige solid,

R_f value: 0.29 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

$C_{25}H_{31}N_6O_3S$ (481.62)

EKA mass spectrum: $(M+H)^+ = 482$

Example 28

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

0.52 g (1.0 mMol) of 1-Methyl-2-[(4-amidinophenyl)-thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride was dissolved in 15 ml ethanol, mixed with 5 ml of 2N sodium hydroxide solution and stirred for 2 hours at room temperature. Then 5 ml of water were added, the alcohol was distilled off, and it was acidified with concentrated hydrochloric acid. The water was distilled off in vacuo, and the crude product was taken up in 5 ml of ethanol and filtered to remove the insoluble sodium chloride. After the solvent had been distilled off the title compound was obtained as a white solid.

Yield: 0.43 g (88% of theory),

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

$C_{23}H_{27}N_5O_3S$ (453.57)

EKA mass spectrum: $(M+H)^+ = 454$

$(M+Na)^+ = 476$

Example 29

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-methylpropyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 27 from 1-methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-(N-(2-methylpropyl-N-(2-ethoxycarbonylethyl)-amide,

ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 83 % of theory,
$C_{25}H_{31}N_6O_3S$ (495.65)
R_f value: 0.30 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5) :
EKA mass spectrum: $(M+H)^+$ = 496

Example 30

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 27 from 1-methyl-2-[(4-cyanophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 90 % of theory,
$C_{28}H_{29}N_5O_3S$ (515.64)
R_f value:0.24 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)
EKA mass spectrum: $(M+H)^+$ = 516
$(M+H+Na)^{++}$ = 269.7

Example 31

1-Methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 28 from 1-methyl-2-[(4-amidinophenyl)thiomethyl-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 76 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.31 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 488

$(M+Na)^+$ = 510

Example 32

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methyl-piperidin-4-yl)-N-methyl-amide-hydrochloride

a) 4-Chloro-3-nitrobenzenesulphonic acid-N-(1-methyl-piperidin-4-yl)-N-methyl-amide

To a solution of 2.2 ml (15 mMol) of 1-methyl-4-methylamino-piperidine in 60 ml pyridine, 3.8 g (15 mMol) of 4-chloro-3-nitro-benzenesulphonic acid chloride were added, in batches, whilst cooling with ice. The mixture was then stirred for two hours with cooling, then evaporated to dryness, the residue was mixed with about 50 ml of water and made alkaline with concentrated ammonia whilst stirring vigorously. The crude product precipitated was suction filtered and purified by column chromatography (250 g silica gel, eluant: dichloromethane with 1.5% ethanol).

Yield: 1.6 g (31% of theory),

$C_{13}H_{18}ClN_3O_4S$ (347.8)

R_f value: 0.19 (silica gel; dichloromethane/ethanol = 19:1)

b) 4-Methylamino-3-nitrobenzenesulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide

1.6 g (4.6 mMol) of 4-chloro-3-nitrobenzenesulphonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide was mixed with 30 ml of 40% methylamine solution and stirred in a sealed flask for four hours at room temperature. Then the mixture was diluted with about 40 ml of water, the product precipitated was suction filtered, washed with water and dried.

Yield: 1.5 g (95% of theory),
$C_{14}H_{22}N_4O_4S$ (343.4)
R_f value: 0.45 (silica gel; dichloromethane/ethanol = 4:1)

c) 3-Amino-4-methylaminobenzenesulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide

1.5 g (4.4 mMol) of 4-methylamino-3-nitrobenzenesulphonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide were dissolved in 100 ml methanol and catalytically hydrogenated at room temperature and under 5 bar hydrogen pressure (10% palladium on charcoal). Then the catalyst was filtered off and the filtrate was evaporated down. The resulting oily product was further reacted without any purification.
Yield: 1.4 g (100% of theory),
$C_{14}H_{24}N_4O_2S$ (312.4)
R_f value: 0.33 (silica gel; dichloromethane/ethanol = 4:1)

d) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulfonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide

532 mg (3.0 mMol) of 4-cyanophenyloxyacetic acid and 486 mg (3.0 mMol) of 1,1'-carbonyldiimidazole were dissolved in 40 ml of tetrahydrofuran and refluxed for 15 minutes. Then 700 mg (2.24 mMol) of 3-amino-4-methylaminobenzenesulphonic acid-N-methyl-N-(1-methyl-piperidin-4-yl)-amide were added and boiling was continued for a further eight hours. Then the mixture was evaporated down and the resulting oily residue was refluxed in 30 ml of glacial acetic acid for one hour. The glacial acetic acid was distilled off, the residue was mixed with about 30 ml of water and made alkaline with concentrated ammonia, and the solution was extracted three times with about 20 ml of dichloromethane. The organic phases were dried and evaporated down. The resulting product was further reacted without any purification.
Yield: 400 mg (39% of theory),
$C_{23}H_{27}N_5O_3S$ (453.6)
R_f value: 0.37 (silica gel; dichloromethane/ethanol = 4:1)

e) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide-hydrochloride

Prepared analogously to Example 25d from 400 mg of 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-(1-methylpiperidin-4-yl)-amide with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 370 mg (83% of theory),
$C_{23}H_{30}N_6O_3S$ (470.6)

EKA mass spectrum: $(M+H)^+$ = 471
$(M+2H)^{++}$ = 236

Example 33

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-phenyl-amide-hydrochloride

---

Prepared analogously to Example 32 from 1-methyl-2-[(4-cyanophenyl)-oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-methyl-N-phenyl-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 46 % of theory,
$C_{23}H_{23}N_5O_3S$ (449.5)

EKA mass spectrum: $(M+H)^+$ = 450
$(M+H+Methanol)^+$ = 482
$(M+2H)^{++}$ = 223

Example 34

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-(3-ethoxycarbonyl-n-propyl)-N-phenyl-amide-hydrochloride

---

Prepared analogously to Example 32 from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-N-

(3-ethoxycarbonyl-n-propyl)-N-phenyl-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 57 % of theory,
$C_{28}H_{31}N_5O_5S$ (549.7)
EKA mass spectrum: $(M+H)^+ = 550$

Example 35

1-Methyl-2-[(3-amidinophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-pyrrolidide-hydrochloride

---

Prepared analogously to Example 32 from 1-methyl-2-[(3-cyanophenyl)oxymethyl]-benzimidazol-5-yl-sulphonic acid-pyrrolidide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 71 % of theory,
$C_{20}H_{23}N_5O_3S$ (413.5)
EKA mass spectrum: $(M+H)^+ = 414$

Example 36

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-methoxycarbonylpropyl)-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butyloxycarbonylpropyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate.
Yield: 83.5 % of theory,
R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)
$C_{29}H_{31}N_5O_3$ (497.6)
EKA mass spectrum: $(M+H)^+ = 498$
$(M+H+Na)^{++} = 260.7$

Example 37

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-methoxycarbonylpropyl)-amide-dihydrochloride and sodium hydroxide solution.
Yield: 92 % of theory,
R_f value: 0.09 (silica gel; dichloromethane/ethanol = 4:1)
$C_{28}H_{29}N_5O_3$ (483.6)

EKA mass spectrum: $(M+H)^+$ = 484
$(M+Na)^+$ = 506
$(M+H+Na)^{++}$ = 253.7

Example 38

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride

---

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butyloxy-carbonylpropyl)-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-glycine and 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(3-tert.butyloxycarbonylpropyl)-amide.
Yield: 65 % of theory,
R_f value: 0.17 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-tert.butyloxycarbonylpropyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 68 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

$C_{29}H_{32}N_6O_3$ (512.6)

EKA mass spectrum: $(M+H)^+$ = 513

$(M+H+Na)^{++}$ = 268

Example 39

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-ethoxycarbonylpropyl)-amide-dihydrochloride and sodium hydroxide solution.

Yield: 73.5 % of theory,

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485

$(M+2H)^{++}$ = 243

$(M+H+Na)^{++}$ = 254

Example 40

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-

phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 73 % of theory,
R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)
$C_{28}H_{29}N_5O_3$ (483.6)

EKA mass spectrum: $(M+H)^+$ = 484
$(M+H+Na)^{++}$ = 253.7

Example 41

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 97 % of theory,
$C_{26}H_{25}N_5O_3$ (455.5)

EKA mass spectrum: $(M+H)^+$ = 456
$(M+Na)^+$ = 478
$(M+2Na)^{++}$ = 250.6

Example 42

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 76 % of theory,
R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{27}N_5O_4$ (485.6)

EKA mass spectrum: $(M+H)^+$ = 486

$(M+H+Na)^{++}$ = 254.7

Example 43

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 58 % of theory,

$C_{25}H_{23}N_5O_4$ (457.5)

EKA mass spectrum: $(M+H)^+$ = 458

$(M+Na)^+$ = 480

$(M+2Na)^{++}$ = 251.6

Example 44

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 74 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485

$(M+H+Na)^{++}$ = 254

Example 45

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 84 % of theory,
$C_{25}H_{24}N_6O_3$ (456.5)
EKA mass spectrum: $(M+H)^+$ = 457
$(M+Na)^+$ = 479
$(M+2Na)^{++}$ = 251

Example 46

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-pyrimidyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-pyrimidyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 14 % of theory,
$C_{26}H_{27}N_7O_4$ (501.6)
Mass spectrum: $(M+H)^+$ = 502

Example 47

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 44 % of theory,

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

$C_{26}H_{26}N_6O_4$ (486.5)

EKA mass spectrum: $(M+H)^+$ = 487

$(M+2H)^{++}$ = 244

$(M+H+Na)^{++}$ = 255

Example 48

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{24}H_{22}N_6O_4$ (458.5)

EKA mass spectrum: $(M+H)^+$ = 459

$(M+Na)^+$ = 481

$(M+2Na)^{++}$ = 252

Example 49

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

---

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-glycine and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide.

Yield: 24 % of theory,

R_f value: 0.56 (silica gel; dichloromethane/methanol = 4:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 70 % of theory,

R_f value: 0.16 (silica gel; dichloromethane/ethanol = 4:1)

$C_{26}H_{27}N_7O_3$ (485.6)

EKA mass spectrum: $(M+H)^+$ = 486

$(M+2H)^{++}$ = 243.7

$(M+H-Na)^{++}$ = 254.6

Example 50

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution.
Yield: 91 % of theory,
$C_{24}H_{23}N_7O_3$ (457.5)

EKA mass spectrum: $(M+H)^+$ = 458
$(M+Na)^+$ = 480
$(M+2Na)^{++}$ = 251.7

Example 51

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 90 % of theory,
R_f value: 0.17 (silica gel; dichloromethane/ethanol = 4:1)
$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485
$(M+2H)^{++}$ = 243
$(M+H+Na)^{++}$ = 254

Example 52

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-dihydrochloride and sodium hydroxide solution.
Yield: 89 % of theory,
$C_{25}H_{24}N_6O_3$ (456.5)
EKA mass spectrum: $(M+H)^+$ = 457
$(M+Na)^+$ = 479

Example 53

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxyarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate.
Yield: 87 % of theory,
R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)
$C_{27}H_{28}N_6O_3$ (484.6)
EKA mass spectrum: $(M+H)^+$ = 485
$(M+2H)^{++}$ = 243
$(M+H+Na)^{++}$ = 254

Example 54

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 79.5 % of theory,
$C_{28}H_{29}N_5O_4$ (499.6)
R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 500.0
$(M+H+Na)^{++}$ = 261.7

Example 55

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 82 % of theory,
$C_{26}H_{25}N_5O_4$ (471.5)
R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 472
$(M+H+Na)^{++}$ = 247.6
$(M+Na)^+$ = 494
$(M+2Na)^{++}$ = 258.6

Example 56

1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 1-Methyl-2-[2-(2-cyanothiophen-5-yl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 25c from 3-(2-cyanothiophen-5-yl)-propionic acid and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide.

Yield: 18 % of theory,

R_f value: 0.66 (silica gel; dichloromethane/methanol = 9:1)

b) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(2-cyanothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 53 % of theory,

$C_{26}H_{28}N_6O_3S$ (504.6)

R_f value: 0.22 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 505

$(M+H+Na)^{++}$ = 264

Example 57

1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 98 % of theory,
$C_{24}H_{24}N_6O_3S$ (476.6)
EKA mass spectrum: $(M+H)^+$ = 477
$(M+Na)^+$ = 499
$(M+2H)^{++}$ = 239

Example 58

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide
Prepared analogously to Example 25c from N-(4-cyanophenyl)-glycine and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide.
Yield: 61 % of theory,
R_f value: 0.62 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic

acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 71 % of theory,

$C_{27}H_{29}N_7O_3$ (499.6)

R_f value: 0.28 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 500

$(M+H+Na)^{++}$ = 261.8

$(M+2H)^{++}$ = 250.8

Example 59

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 91 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+H+Na)^{++}$ = 247.6

$(M+2H)^{++}$ = 236.7

$(M+2Na)^{++}$ = 258.6

Example 60

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 1-Methyl-2-[2-(4-cyanophenyl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 149a from 3-(4-cyanophenyl)-propionic acid and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide.
Yield: 22 % of theory,
R_f value: 0.68 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 85 % of theory,
$C_{28}H_{30}N_6O_3$ (498.6)
R_f value: 0.30 (silica gel; dichloromethane/methanol = 5:1)
EKA mass spectrum: $(M+H)^+$ = 499
$(M+H+Na)^{++}$ = 261

Example 61

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 97 % of theory,
$C_{26}H_{26}N_6O_3$ (470.5)
EKA mass spectrum: $(M+H)^+$ = 471
$(M+H+Na)^{++}$ = 247
$(M+Na)^+$ = 493

Example 62

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 86 % of theory,
$C_{29}H_{31}N_5O_3$ (497.6)
R_f value: 0.11 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 498
$(M+2H)^{++}$ = 249.8

Example 63

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 71 % of theory,
$C_{27}H_{27}N_5O_3$ (469.6)
EKA mass spectrum: $(M+H)^+$ = 470
$(M+H+Na)^{++}$ = 246.6
$(M+Na)^+$ = 492
$(M+2H)^{++}$ = 235.6

Example 64

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(methoxycarbonylmethyl)-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(methoxycarbonylmethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 73 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+H+Na)^{++}$ = 247.8

Example 65

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide and methanolic hydrochloric acid, methanol and ammonium carbonate.

Yield: 78 % of theory,

$C_{26}H_{27}N_7O_3$ (485.6)

R_f value: 0.31 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 486

$(M+H+Na)^{++}$ = 254.8

Example 66

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide-hydrochloride

---

a) 1-Methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide

Prepared analogously to Example 25c from 3-(4-cyanophenyl)-propionic acid and 3-amino-4-methylamino-benzoic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide.

Yield: 67 % of theory,

IR Mass spectrum (KBr): characteristic bands at

3439.5 cm^{-1} (N-H); 2235.5 cm^{-1} C≡N);

1631.6 cm^{-1} (C=O)

b) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 92 % of theory,

$C_{27}H_{27}N_9O$ (493.6)

EKA mass spectrum: $(M+H)^+$ = 494

$(M+Na)^+$ = 516

$(M+2H)^{++}$ = 258.7

Example 67

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 29 % of theory,

$C_{26}H_{26}N_{10}O$ (494.6)

EKA mass spectrum: $(M+H)^+$ = 495

Example 68

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-n-hexyloxycarbonylethyl)-amide-hydrochloride

---

0.60 g (1.1 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride were added to about 30 ml of n-hexanol saturated with hydrogen chloride and the mixture was stirred for 19 hours at room temperature. Then the hexanol was distilled off *in vacuo*, the residue was mixed with about 5 ml of 1N ammonia solution with stirring and evaporated down once more. The crude product thus obtained was purified by column chromatography (silica gel, dichloromethane/methanol = 5:1).

Yield: 53 % of theory,

$C_{31}H_{37}N_7O_3$ (555.7)

R_f value: 0.36 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 556

Example 69

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-N-methylglycine and 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide.

Yield: 71 % of theory,

R_f value: 0.66 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 77 % of theory,

$C_{28}H_{31}N_7O_3$ (513.6)

EKA mass spectrum: $(M+H)^+$ = 514

$(M+H+Na)^{++}$ = 268.7

Example 70

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 66 % of theory,
$C_{26}H_{27}N_7O_3$ (485.6)
EKA mass spectrum: $(M+H)^+$ = 486
$(M+Na)^+$ = 508
$(M+2Na)^{++}$ = 265.6

Example 71

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 65 % of theory,
$C_{28}H_{35}N_5O_3$ (489.6)
EKA mass spectrum: $(M+H)^+$ = 490

Example 72

1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 89 % of theory,

$C_{26}H_{31}N_5O_3$ (461.6)

EKA mass spectrum: $(M+H)^+$ = 462

$(M+H+Na)^{++}$ = 242.6

$(M+Na)^+$ = 484

$(M+2H)^{++}$ = 231.6

Example 73

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 60 % of theory,

$C_{27}H_{34}N_6O_3$ (490.6)

EKA mass spectrum: $(M+H)^+$ = 491

Example 74

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-cyclopentyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 45 % of theory,
$C_{25}H_{30}N_3O_4$ (462.6)

EKA mass spectrum: $(M+H)^+$ = 463
$(M+H+Na)^{++}$ = 243
$(M+Na)^+$ = 485
$(M+2Na)^{++}$ = 254

Example 75

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 54 % of theory,
$C_{27}H_{29}N_7O_3$ (499.6)

EKA mass spectrum: $(M+H)^+$ = 500
$(M+2H)^{++}$ = 250.7

Example 76

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylmethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 68 % of theory,
$C_{25}H_{25}N_7O_3$ (471.5)
EKA mass spectrum: $(M+H)^+$ = 472
$(M+Na)^+$ = 494
$(M+2Na)^{++}$ = 258.6

Example 77

1-Methyl-2-[2-(4-amidinophenyl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[2-(4-cyanophenyl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 91 % of theory,
$C_{28}H_{30}N_6O_3$ (498.6)
R_f value: 0.19 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 499

Example 78

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 86 % of theory,

$C_{27}H_{29}N_7O_3$ (499.6)

R_f value: 0.09 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 500

Example 79

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-dihydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{25}H_{25}N_7O_3$ (471.5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+2H)^{++}$ = 236.6

$(M+2Na)^{++}$ = 258.6

Example 80

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-Methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 64 % of theory,

$C_{28}H_{31}N_7O_3$ (513.6)

EKA mass spectrum: $(M+H)^+$ = 514

Example 81

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 70 % of theory,

$C_{26}H_{27}N_7O_3$ (485.6)

EKA mass spectrum: $(M+H)^+$ = 486

$(M+Na)^+$ = 508

$(M+2Na)^{++}$ = 265.6

Example 82

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 1-Methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

Prepared analogously to Example 25c from N-(4-cyanophenyl)-N-methylglycine and 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide.

Yield: 71 % of theory,

R_f value: 0.38 (silica gel; dichloromethane/methanol = 19:1)

b) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 74 % of theory,

$C_{29}H_{32}N_6O_3$ (512.6)

EKA mass spectrum: $(M+H)^+$ = 513

$(M+H+Na)^{++}$ = 268

$(M+2H)^{++}$ = 257

Example 83

1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 80 % of theory,
$C_{27}H_{28}N_6O_3$ (484.6)
EKA mass spectrum: $(M+H)^+$ = 485
$(M+H+Na)^{++}$ = 254
$(M+Na)^+$ = 507
$(M+2Na)^+$ = 265

Example 84

1-ethyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-ethyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 85 % of theory,
$C_{28}H_{31}N_7O_3$ (513.6)
R_f value: 0.21 (silica gel; dichloromethane/methanol = 5:1)
EKA mass spectrum: $(M+H)^+$ = 514
$(M+H+Na)^{++}$ = 268.6
$(M+2H)^{++}$ = 257.7

Example 85

1-ethyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-ethyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and 2N sodium hydroxide solution.
Yield: 49 % of theory,
$C_{26}H_{27}N_7O_3$ (485.6)
EKA mass spectrum: $(M+H)^+$ = 486
$(M+H+Na)^{++}$ = 254.6
$(M+2H)^{++}$ = 243.6
$(M+2Na)^{++}$ = 265.7

Example 86

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 88 % of theory,
$C_{28}H_{29}FN_6O_3$ (516.6)
R_f value: 0.08 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 517
$(M+H+Na)^{++}$ = 270
$(M+2H)^{++}$ = 259

Example 87

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 45 % of theory,
$C_{26}H_{25}FN_6O_3$ (488.5)
R_f value: 0.05 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 489
$(M+H+Na)^{++}$ = 267
$(M+2H)^{++}$ = 256

Example 88

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 79 % of theory,
$C_{29}H_{32}N_6O_3$ (512.6)
R_f value: 0.10 (silica gel; dichloromethane/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 513
$(M+H+Na)^{++}$ = 268

Example 89

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-methylphenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 62 % of theory,
$C_{27}H_{28}N_6O_3$ (484.6)

EKA mass spectrum: $(M+H)^+$ = 485
$(M+H+Na)^{++}$ = 254
$(M+Na)^+$ = 507
$(M+2Na)^{++}$ = 265

Example 90

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

1.1 g (2.06 mMol) of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride was dissolved in a mixture of 40 ml of tetrahydrofuran and 10 ml of water, then 570 mg (4.12 mMol) of potassium carbonate and 362 mg (2.2 mMol) of n-hexyl chloroformate were added and stirred for two hours at room temperature. The solvent was then distilled off, the residue was mixed with about 50 ml of saturated saline solution and the resulting solution was extracted three times with 20 ml of dichloromethane. The extracts were dried over sodium sulphate and evaporated down. The crude product thus obtained was purified by column chromatography (100 g silica gel; dichloromethane + 5% ethanol).

Yield: 78 % of theory,

$C_{35}H_{42}N_6O_5$ (626.8)

R_f value: 0.49 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 627

$(M+H+Na)^{++}$ = 325

$(M+2H)^{++}$ = 314

Example 91

1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and methyl chloroformate.

Yield: 41 % of theory,

$C_{30}H_{32}N_6O_5$ (556.6)

R_f value: 0.85 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 557

$(M+H+Na)^{++}$ = 290

$(M+Na)^+$ = 579

Example 92

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and ethyl chloroformate.

Yield: 62 % of theory,

$C_{30}H_{32}N_6O_5$ (556.6)

R_f value: 0.51 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 557

$(M+H+Na)^{++}$ = 290

$(M+2H)^{++}$ = 279

Example 93

1-Methyl-2-[N-[4-(N-cyclohexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and cyclohexyl chloroformate.

Yield: 25 % of theory,

$C_{34}H_{38}N_6O_5$ (610.7)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 611

$(M+2H)^{++}$ = 306

Example 94

1-Methyl-2-[N-[4-[N-[2-(methylsulphonyl)ethyloxycarbonyl]-amidino]phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate.

Yield: 66 % of theory,

$C_{32}H_{36}N_6O_7S$ (648.8)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 649

$(M+H+Na)^{++}$ = 336

$(M+2H)^{++}$ = 325

Example 95

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.
Yield: 41 % of theory,
$C_{36}H_{44}N_6O_5$ (640.8)
R_f value: 0.43 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 641
$(M+Na)^+$ = 663

Example 96

1-Methyl-2-[N-[4-(N-hydroxylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

1.44 g (3.0 mMol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, 0.625 g (9.0 mMol) of hydroxylamine hydrochloride and 0.425 g (4.0 mMol) of sodium carbonate were dissolved in 80 ml of ethanol and refluxed for 7 hours. Then a further 210 mg of hydroxylamine hydrochloride and 170 mg of sodium carbonate were added, the mixture was boiled for a further 5 hours and then evaporated down *in vacuo*. The residue was dissolved in about 30 ml of dichloromethane, the solution obtained was washed with 20 ml of water, the organic phase was dried and evaporated down. The crude product thus

obtained was purified by column chromatography (200 g silica gel, dichloromethane + 4% ethanol).
Yield: 39 % of theory,
$C_{28}H_{30}N_6O_4$ (514.6)
R_f value: 0.15 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 515
$(M+Na)^+$ = 537
$(2M+H)^+$ = 1029
$(2M+Na)^+$ = 1051

Example 97

1-Methyl-2-[N-[4-(N-n-heptyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate.
Yield: 43 % of theory,
$C_{35}H_{42}N_6O_5$ (626.8)
R_f value: 0.40 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 627
$(M+H+Na)^{++}$ = 325
$(M+Na)^+$ = 649

Example 98

1-Methyl-2-[N-[4-(N-benzoylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic

acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride.
Yield: 88 % of theory,
$C_{34}H_{32}N_6O_4$ (588.7)
R_f value: 0.37 (silica gel; dichloromethane/ethanol = 19:1)
^{1}H-NMR spectrum (D_6-DMSO): 2.61 (t,2H), 3.54 (s,3H), 3.76 (s,3H), 4.10 (t,2H), 4.61 (d,2H), 6.83 (d,2H), 7.05 to 7.55 (m,12H),8.03 (d,2H), 8.25 (dd,2H), 8.98 (s,1H), 10.48 (s,1H)

Example 99

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.
Yield: 54 % of theory,
$C_{34}H_{40}N_6O_5$ (612.7)
R_f value: 0.45 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 613

Example 100

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-n-propyloxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-n-propyloxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.
Yield: 31 % of theory,

$C_{36}H_{44}N_6O_5$ (640.8)

R_f value: 0.42 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 641

$(M+H+Na)^{++}$ = 332

$(M+Na)^+$ = 663

Example 101

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and ethyl chloroformate.

Yield: 72 % of theory,

$C_{29}H_{31}N_7O_5$ (557.6)

R_f value: 0.58 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 558

$(M+H+Na)^{++}$ = 290.8

$(M+Na)^+$ = 580

Example 102

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.

Yield: 57 % of theory,

$C_{35}H_{43}N_7O_5$ (641.8)

R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 642

$(M+H+Na)^{++}$ = 332.8

$(M+Na)^+$ = 664

Example 103

1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and methyl chloroformate.

Yield: 48 % of theory,

$C_{29}H_{31}N_7O_5$ (557.6)

R_f value: 0.62 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 558

$(M+H+Na)^{++}$ = 290.7

$(M+Na)^+$ = 580

Example 104

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)phenyl]-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

0.7 g (1.1 mMol) of 1-methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide was stirred in a mixture of 0.12 g (3.0 mMol) of sodium hydroxide, 5 ml of water and 10 ml of methanol for one hour at room temperature. Then the mixture was diluted with 20 ml of water and adjusted to pH 6 with glacial acetic acid. Then about 5 ml of

diethylether were added and the mixture was vigourously stirred for one hour. The product thus precipitated was suction filtered, washed with a little water, then with diethylether and dried.

Yield: 80 % of theory,

$C_{34}H_{41}N_7O_5$ (627.8)

EKA mass spectrum: $(M+H)^+$ = 628

$(M+H+Na)^{++}$ = 325.7

$(M+Na)^+$ = 650

$(M+2Na)^{++}$ = 337.7

Example 105

1-Methyl-2-[N-[4-[N-(2-methylsulphonyl-ethyloxycarbonyl)amidino]-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate.

Yield: 65 % of theory,

$C_{31}H_{35}N_7O_7S$ (649.7)

R_f value: 0.54 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 650

$(M+H+Na)^{++}$ = 336.6

$(M+Na)^+$ = 672

$(M+2Na)^{++}$ = 347.6

Example 106

1-Methyl-2-[N-[4-(N-n-butyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-butyl chloroformate.

Yield: 30 % of theory,

$C_{31}H_{35}N_7O_5$ (585.7)

R_f value: 0.62 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 586

$(M+H+Na)^{++}$ = 304.7

$(M+2H)^{++}$ = 293.7

Example 107

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.

Yield: 51 % of theory,

$C_{33}H_{39}N_7O_5$ (613.7)

R_f value: 0.56 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 614

$(M+H+Na)^{++}$ = 318.7

$(M+2H)^{++}$ = 307.6

Example 108

1-Methyl-2-[N-[4-(N-n-heptyloxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate.
Yield: 21 % of theory,
$C_{34}H_{41}N_7O_5$ (627.8)
R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 628
$(M+H+Na)^{++}$ = 325.7
$(M+2H)^{++}$ = 314.7

Example 109

1-Methyl-2-[N-[4-(N-n-pentyloxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate.
Yield: 66 % of theory,
$C_{32}H_{37}N_7O_5$ (599.7)
R_f value: 0.58 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 600
$(M+H+Na)^{++}$ = 311.7
$(M+Na)^+$ = 622

Example 110

1-Methyl-2-[N-[4-(N-n-nonyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and n-nonyl chloroformate.
Yield: 60 % of theory,
$C_{36}H_{45}N_7O_5$ (655.8)
R_f value: 0.48 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 656
$(M+H+Na)^{++}$ = 339.8
$(M+Na)^+$ = 678

Example 111

1-Methyl-2-[N-[4-(N-benzoylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride.
Yield: 62 % of theory,
$C_{33}H_{31}N_7O_4$ (589.7)
R_f value: 0.50 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 590
$(M+Na)^+$ = 612

Example 112

1-Methyl-2-[N-[4-(N-nicotinoylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and nicotinic acid chloride.
Yield: 40 % of theory,
$C_{32}H_{30}N_8O_4$ (590.7)
R_f value: 0.47 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 591
$(M+H+Na)^{++}$ = 307
$(M+Na)^+$ = 613

Example 113

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.
Yield: 51 % of theory,
$C_{34}H_{41}N_7O_5$ (627.8)
R_f value: 0.53 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 628
$(M+H+Na)^{++}$ = 325.7
$(M+2H)^{++}$ = 314.7

Example 114

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.
Yield: 57 % of theory,
$C_{36}H_{45}N_7O_5$ (655.8)
R_f value: 0.46 (silica gel; dichloromethane/methanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 656
$(M+H+Na)^{++}$ = 339.7
$(M+2H)^{++}$ = 328.7

Example 115

1-Methyl-2-[N-[4-[N-(2-methylsulphonyl-ethyloxycarbonyl)amidino]-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide-hydrochloride and 2-(methylsulphonyl)-ethyl chloroformate.
Yield: 72 % of theory,
$C_{30}H_{33}N_7O_7S$ (635.7)
R_f value: 0.23 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 636
$(M+H+Na)^{++}$ = 329.8

Example 116

1-Methyl-2-[N-[4-(N-cyclohexyloxycarbonylamidino)-phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-hydrochloride and cyclohexyl chloroformate.
Yield: 40 % of theory,
$C_{32}H_{35}N_7O_5$ (597.7)
R_f value: 0.26 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 598
$(M+Na)^+$ = 620

Example 117

1-Methyl-2-[N-[4-(N-methoxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-ethoxycarbonylmethyl-amide-hydrochloride and methyl chloroformate.
Yield: 62 % of theory,
$C_{28}H_{29}N_7O_5$ (543.6)
R_f value: 0.19 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 544
$(M+H+Na)^{++}$ = 283.8
$(M+Na)^+$ = 566

Example 118

1-Methyl-2-[N-[4-(N-ethoxycarbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-methoxycarbonylmethyl-amide-hydrochloride and ethyl chloroformate.
Yield: 42 % of theory,
$C_{28}H_{29}N_7O_5$ (543.6)
R_f value: 0.20 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 544

Example 119

1-Methyl-2-[N-[4-(N-n-octyloxycarbonyl-amidino)-phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.
Yield: 35 % of theory,
$C_{36}H_{45}N_7O_5$ (655.8)
R_f value: 0.28 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 656
$(M+2H)^{++}$ = 328.7

Example 120

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)-phenyl]-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.
Yield: 58 % of theory,
$C_{35}H_{43}N_7O_5$ (641.2)
R_f value: 0.42 (silica gel; dichloromethane/ethanol = 19:1)
EKA mass spectrum: $(M+H)^+$ = 642
$(M+H+Na)^{++}$ = 332.7

Example 121

1-Methyl-2-[N-[4-(N-n-octyloxycarbonylamidino)-phenyl]-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.
Yield: 36 % of theory,
$C_{37}H_{47}N_7O_5$ (669.8)
EKA mass spectrum: $(M+H)^+$ = 670
$(M+H+Na)^{++}$ = 346.8
$(M+2H)^{++}$ = 335.6

Example 122

1-Methyl-2-[N-[4-(N-n-butyloxycarbonylamidino)-phenyl]-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-butyl chloroformate.
Yield: 34 % of theory,
$C_{33}H_{39}N_7O_5$ (613.7)

EKA mass spectrum: $(M+H)^+$ = 614
$(M+H+Na)^{++}$ = 318.7
$(M+Na)^+$ = 636

Example 123

1-Methyl-2-[N-[4-(N-benzoylamidino)phenyl]-N-methyl-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride.
Yield: 63 % of theory,
$C_{35}H_{35}N_7O_4$ (617.7)

EKA mass spectrum: $(M+H)^+$ = 618
$(M+H+Na)^{++}$ = 320.7
$(M+Na)^+$ = 640

Example 124

1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-(1-ethoxycarbonylmethyl-cyclohex-1-yl)-ketone-hydrochloride

a) 4-Chlorophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

8.4 g (40 mMol) of 3-(4-chlorobenzoyl)-propionic acid were dissolved in 300 ml of tetrahydrofuran and 5.8 g (120 mMol) of sodium hydride (50-60% suspension in paraffin oil) were added in batches. Then the mixture was refluxed for 1.5 hours with stirring, after which 8.9 ml (60 mMol) of 1,5-diiodopentane were added dropwise and boiling was continued for a further three hours. After cooling the solution was stirred into 200 ml of ice-water, then the tetrahydrofuran was distilled off *in vacuo*, the resulting aqueous solution was acidified with 2N hydrochloric acid and extracted three times with 150 ml of dichloromethane. The organic phase was dried and evaporated down, the crude product thus obtained was purified by column chromatography (500 g silica gel; eluant: dichloromethane with 1-2% ethanol).
Yield: 6.2 g (55% of theory) of oily product,
$C_{15}H_{17}ClO_3$ (280.8)
R_f value: 0.56 (silica gel; dichloromethane/ethanol = 19:1)

b) 4-Chloro-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

7.0 g (25 mMol) of 4-chlorophenyl-(1-hydroxycarbonyl-methylcyclohex-1-yl)-ketone were added in batches, with stirring, at -5 to -10°C, to 80 ml of fuming nitric acid. The solution was then stirred for a further 10 minutes, then stirred into 200 ml of ice-water, the precipitated product was then washed with water and dried.
Yield: 7.8 g (96% of theory),
$C_{15}H_{16}ClNO_5$ (325.8)
R_f value: 0.41 (silica gel; petroleum ether/ethyl acetate 4:6)

c) 4-Methylamino-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone

7.8 g (23.9 mMol) of 4-chloro-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone were stirred in 100 ml of a 40% aqueous methylamine solution at room temperature for 14 hours, then diluted with about 150 ml of water and made slightly acidic with glacial acetic acid. The precipitated product was suction filtered, washed with water and dried.

Yield: 7.1 g (93% of theory),

$C_{16}H_{20}N_2O_5$ (320.4)

R_f value: 0.34 (silica gel; dichloromethane/ethanol = 19:1)

d) 4-Methylamino-3-nitrophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

4.9 g (15 mMol) of 4-methylamino-3-nitrophenyl-(1-hydroxycarbonylmethyl-cyclohex-1-yl)-ketone were dissolved in 100 ml of tetrahydrofuran, 2.4 g (15 mMol) of 1,1'-carbonyl-diimidazole were added and the mixture was refluxed for 15 minutes. Then the solvent was evaporated off, 30 ml of methanol were added and the mixture was boiled for three hours with stirring. After the methanol had been distilled off the crude product thus obtained was purified by column chromatography (250 g silica gel, eluant: dichloromethane with 1 to 5% ethanol).

Yield: 2.4 g (48% of theory),

$C_{17}H_{22}N_2O_5$ (334.4)

R_f value: 0.76 (silica gel; dichloromethane/ethanol = 19:1)

e) 3-Amino-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

2.4 g (7.2 mMol) of 4-methylamino-3-nitrophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone were catalytically hydrogenated in 100 ml of methanol at room temperature under 5 bar hydrogen pressure (10% palladium on

charcoal). The crude product thus obtained was further reacted without purification.
Yield: 2.1 g (96% of theory),
R_f value: 0.34 (silica gel; dichloromethane/ethanol = 19:1)

f) 3-(4-Cyanophenyloxyacetylamino)-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

620 mg (3.5 mMol) of 4-cyanophenyloxyacetic acid and 570 mg (3.5 mMol) of 1,1'-carbonyl-diimidazole were refluxed in 50 ml of tetrahydrofuran for 15 minutes. Then 1.0 g (3.28 mMol) of 3-amino-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone were added and the mixture was boiled for a further 4 hours. Then the solvent was evaporated off and the crude product thus obtained was purified by column chromatography (150 g silica gel; eluant: dichloromethane with 0 to 2% ethanol).
Yield: 1.4 g (93% of theory),
$C_{26}H_{29}N_3O_5$ (463.5)
R_f value: 0.44 (silica gel; dichloromethane/ethanol = 19:1)

g) 1-Methyl-2-[(4-cyanophenyl)oxymethyl]-benzimidazol-5-yl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone

1.4 g (3.02 mMol) of 3-(4-cyanophenyloxyacetylamino)-4-methylaminophenyl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone were refluxed in 50 ml of glacial acetic acid for one hour. Then the glacial acetic acid was distilled off, the residue was mixed with 20 ml of water and made alkaline with concentrated ammonia. This solution was extracted three times with 20 ml of dichloromethane, the organic extracts were dried and evaporated down. The crude product thus obtained was purified by column chromatography (100 g silica gel; eluant: dichloromethane with 0 to 2% ethanol).
Yield: 700 mg (52% of theory),
$C_{26}H_{27}N_3O_4$ (445.5)

h) 1-Methyl-2-[(4-amidinophenyl)oxymethyl]-benzimidazol-5-yl-(1-ethoxycarbonylmethyl-cyclohex-1-yl)-ketone-hydrochloride

Prepared analogously to Example 25d from 700 mg (1.57 mMol) of 1-methyl-2-(4-cyanophenyloxymethyl)-benzimidazol-5-yl-(1-methoxycarbonylmethyl-cyclohex-1-yl)-ketone with ethanolic hydrochloric acid and ammonium carbonate.
Yield: 390 mg (50% of theory),
$C_{27}H_{32}N_4O_4$ (476.6)
EKA mass spectrum: $(M+H)^+ = 477$
^1H-NMR spectrum(d_6-DMSO): 1.10 (t,3H); 1.0-2.15 (m,10H); 3.36 (s,3H); 3.90 (s,2H); 3.94 (q,2H); 5.60 (s,2H); 7.25-7.40 (m,3H); 7.56-7.75 (m,2H); 7.90 (d,2H); 9.20 (broad s,4H) ppm.

Example 125

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-tert.butyl-ketone-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-tert.butyl-ketone, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 59 % of theory,
$C_{21}H_{25}N_5O$ (363.5)
EKA mass spectrum: $(M+H)^+ = 364$

Example 126

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-(1-methylcyclopent-1-yl)-ketone-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-(1-

methylcyclopent-1-yl)-ketone, ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 63.5 % of theory,
$C_{23}H_{27}N_5O$ (389.5)
EKA mass spectrum: $(M+H)^+ = 390$

Example 127

2-[(4-amidinophenyl)sulphinylmethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

A solution of 0.15 g (0.27 mMol) of 2-[(4-amidinophenyl)thiomethyl]-benzothiazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride in 10 ml of acetic acid was mixed with 0.09 ml (about 0.81 mMol) of 30% hydrogen peroxide solution and stirred at room temperature. After 4 days a further 0.18 ml of hydrogen peroxide solution was added and the resulting mixture was stirred for a further two days. After removal of the solvent *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 10:1 to 4:1).
Yield: 58 % of theory,
$C_{27}H_{26}N_4O_4S_2$ (534.66)
R_f value: 0.24 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)
EKA mass spectrum: $(M+H)^+ = 535$

Example 128

1-Methyl-2-[(4-amidinophenyl)sulphonylmethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

A solution of 0.40 g (0.70 mMol) of 1-methyl-2-[(4-amidinophenyl)thiomethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride in 10 ml of formic acid was mixed with 2 ml of 30% hydrogen peroxide solution and the mixture was stirred for 16 hours at room temperature. Then the solvent was distilled off *in vacuo*, whereupon the desired compound was obtained as a beige solid (contaminated with some 1-methyl-2-[(4-amidinophenyl)sulfinylmethyl]-benzimidazol-5-yl-carboxylic acid-N-(n-propyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride).

Yield: 95 % of theory,

$C_{25}H_{31}N_6O_5S$ (513.62)

R_f value: 0.50 (silica gel; ethyl acetate/ethanol/1N hydrochloric acid = 50:45:5)

EKA mass spectrum: $(M+H)^+ = 514$

Example 129

2-[N-(4-amidinophenyl)-aminomethyl]-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) Methyl 5-amino-6-chloro-nicotinate

A solution of 1.08 g (5.00 mMol) of methyl 6-chloro-5-nitro-nicotinate (see A.H. Berrie, G.T. Newbold, F.S. Spring in J. Chem. Soc., 2590, 1951) in 25 ml of absolute ethanol was mixed successively with 0.53 ml (29 mMol) of water, 3.2 g (57 mMol) of iron powder and 0.030 ml of concentrated hydrochloric acid and heated to boiling for one hour. Then equal quantities of water, iron powder and hydrochloric acid were added and the mixture was heated to boiling for 30 minutes. The precipitate formed on cooling was filtered off and washed with ethanol and the solvent was distilled off *in vacuo*.

Yield: 0.75 g (81% of theory) of greenish-yellow solid,
R_f value: 0.31 (silica gel;ethyl acetate/petroleum ether = 1:4)
$C_7H_7ClN_2O_2$ (186.60)
YEF- Mass spectrum: M^+ = 186 and 188 (chlorine isotopes).

b) Methyl 6-chloro-5-methoxyacetamido-nicotinate

A solution of 0.75 g (4.02 mMol) of methyl 5-amino-6-chloro-nicotinate and 0.43 g = 0.35 ml (4.5 mMol) of methoxyacetylchloride in 20 ml of chlorobenzene was stirred for one hour at 110°C. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1), evaporated down again *in vacuo* and then digested with petroleum ether.
Yield: 0.55 g (53% of theory) light yellow amorphous solid,
R_f value: 0.33 (silica gel; ethyl acetate/petroleum ether = 1:4)

c) Methyl 2-methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylate

A mixture of 0.53 g (2.05 mMol) of methyl 6-chloro-5-methoxyacetamido-nicotinate and 0.42 g (1.0 mMol) of Lawessons reagent was refluxed for 16 hours in 25 ml of xylene. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1) and evaporated down again *in vacuo*.
Yield: 0.33 g (67% of theory) of yellow amorphous solid,
R_f value: 0.52 (silica gel; ethyl acetate/petroleum ether = 1:4)

d) 2-Methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid

A mixture of 1.1 g (4.62 mMol) of methyl 2-methoxymethyl-thiazolo[5,4-b]pyridine-6-carboxylate and 9.2 ml of 2N sodium hydroxide solution were stirred into 50 ml of ethanol for one hour at room temperature. Then 9.2 ml of 2N hydrochloric acid were added, the alcohol was distilled off, and it was diluted with 20 ml of water. The aqueous phase was acidified with concentrated hydrochloric acid whilst cooling with ice, the beige precipitate formed was filtered off, then washed with water and dried.
Yield: 1.03 g (100% of theory),
R_f value: 0.10 (silica gel; ethyl acetate/petroleum ether = 3:7)

e) 2-Methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A suspension of 1.03 g (4.62 mMol) of 2-methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid in 40 ml of methylene chloride was mixed with 1.6 g = 1.0 ml (13.5 mMol) of thionyl chloride and refluxed for 90 minutes, during which time the solid gradually dissolved. After the liquid components had been distilled off the crude product was taken up twice more in methylene chloride and concentrated again. The resulting crude acid chloride (1.2 g) was taken up in 40 ml of tetrahydrofuran, added dropwise to a mixture of 0.94 g (4.86 mMol) of N-(2-ethoxy-carbonylethyl)aniline and 2.1 ml (13.8 mMol) of triethylamine in 30 ml of tetrahydrofuran and stirred for 2 hours at room temperature. Then it was diluted with 200 ml of ethyl acetate, washed with 100 ml of 14% saline solution and the organic phase was dried with sodium sulphate. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 100:1).
Yield: 1.57 g (87% of theory) of yellow oil,
R_f value: 0.55 (silica gel; methylene chloride/ethanol = 19:1)

f) 2-[N-(4-Cyanophenyl)-aminomethyl]-thiazolo[5,4-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A mixture of 1.54 g (3.85 mMol) of 2-methoxymethyl-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and 4.3 ml (4.3 mMol) of a 1 molar solution of boron tribromide in methylene chloride was dissolved in a further 30 ml of methylene chloride and stirred for 5 hours at room temperature. Then the mixture was washed with 40 ml of saturated sodium hydrogen carbonate solution, the organic phase was dried with sodium sulphate and the solvent was distilled off. The crude product (1.9 g) was taken up in 15.0 ml of N,N-diisopropyl-ethylamine, mixed with 0.50 g (4.2 mMol) of 4-aminobenzonitrile and heated to boiling for one hour. Then the solvent was distilled off *in vacuo*, the crude product was taken up in 100 ml of methylene chloride, the organic phase was washed with 100 ml of water and dried with sodium sulphate. After the solvent had been removed *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; ethyl acetate/petroleum ether = 35:65 to 1:1) and evaporated down again *in vacuo*.

Yield: 0.45 g (24% of theory) of yellow amorphous solid, R_f value: 0.34 (silica gel; ethyl acetate/petroleum ether = 1:1)

g) 2-[N-(4-amidinophenyl)-aminomethyl]-thiazolo[5,4-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

0.39 g (0.803 mMol) of 2-[N-(4-cyanophenyl)-aminomethyl]-thiazolo[5,4-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 40 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C and then at room temperature, until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue was taken up in 40 ml

of absolute ethanol and mixed with 0.5 g ammonium carbonate. After 18 hours the solvent was removed *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).

Yield: 78 % of theory of yellow foam,

$C_{26}H_{26}N_6O_3S$ (502.60)

R_f value: 0.19 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+ = 503$

Example 130

1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-2-mercapto-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A solution of 6.5 g (19 mMol) of 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and 4.5 g (22.8 mMol) of N,N'-thiocarbonyldiimidazole were dissolved in 100 ml of tetrahydrofuran under a nitrogen atmsphere, the solution was heated to 90°C for 4 hours and left to stand for 16 hours at room temperature. After removal of the solvent *in vacuo* the crude product obtained was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate = 100:0 to 65:35).

Yield: 6.8 g (93 % of theory) of beige crystalline solid,

R_f value: 0.55 (silica gel; ethyl acetate)

b) 1-Methyl-2-[(4-cyanophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

A solution of 1.30 g (3.4 mMol) of 1-methyl-2-mercapto-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, 0.52 g (3.74 mMol) of potassium

carbonate and 0.66 g (3.4 mMol) of 4-bromomethylbenzonitrile were dissolved in 40 ml of absolute ethanol, stirred for 4 hours at 60°C and 16 hours at room temperature. Then the solvent was distilled off *in vacuo*, the crude product was taken up in 30 ml of methylene chloride, washed with 40 ml of water and dried with sodium sulphate. After filtration and distillation of the solvent the desired compound was obtained as a beige-white solid.
Yield: 1.8 g (100 % of theory),
R_f value: 0.64 (silica gel; ethyl acetate)

c) 1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

1.5 g (3.0 mMol) of 1-methyl-2-[(4-cyanophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were stirred in 80 ml of ethanol saturated with hydrogen chloride for 6.5 hours first at 0°C, then at room temperature, until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum bath temperature of 30°C, the oily residue taken up in 80 ml of absolute ethanol and mixed with 1.0 g (10.5 mMol) of ammonium carbonate. After 18 hours the solvent was distilled off *in vacuo* and the crude product obtained was purified by flash chromatography (silica gel; methylene chloride/ethanol = 19:1 to 10:1).
Yield: 78 % of theory of light beige solid,
$C_{28}H_{29}N_5O_3S$ (515.63)
R_f value: 0.19 (silica gel; methylene chloride/ethanol = 4:1)
EKA mass spectrum: $(M+H)^+$ = 516
$(M+H+Na)^{++}$ = 269.7
$(M+2H)^{++}$ = 258.7

Example 131

1-Methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 10 from 1-methyl-2-[(4-amidinophenyl)methylthio]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 57 % of theory,

$C_{26}H_{25}N_5O_3S$ (487.58)

R_f value: 0.23 (Reversed Phase silica gel RP-8; Methanol/5% saline solution = 6:4)

EKA mass spectrum: $(M+H)^+$ = 488

$(M+Na)^+$ = 510

$(M+Na+H)^{++}$ = 255.6

Example 132

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-propargyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-propargyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 81 % of theory,

$C_{25}H_{28}N_6O_3$ (460.6)

R_f value: 0.094 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 461

$(M+H+Na)^{++}$ = 242

$(M+2H)^{++}$ = 231

Example 133

1-Methyl-2-[2-[4-(N-n-hexyloxycarbonylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-hexyl chloroformate.

Yield: 72 % of theory,

$C_{35}H_{42}N_6O_5$ (626.8)

R_f value: 0.54 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 627

$(M+Na)^+$ = 649

Example 134

1-Methyl-2-[2-[4-(N-benzoylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and benzoyl chloride.

Yield: 79 % of theory,

$C_{35}H_{34}N_6O_4$ (602.7)

R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 603

$(M+Na)^+$ = 625

Example 135

1-Methyl-2-[2-[4-(N-nicotinoylamidino)phenyl]ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and nicotinic acid chloride.

Yield: 56 % of theory,

$C_{34}H_{33}N_7O_4$ (603.7)

R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 604

$(M+Na)^+$ = 626

Example 136

1-Cyclopropyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-Cyclopropyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 31 % of theory,

$C_{30}H_{33}N_6O_3$ (524.6)

R_f value: 0.40 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 525

$(M+H+Na)^{++}$ = 274

$(M+2H)^{++}$ = 263

Example 137

1-Cyclopropyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-cyclopropyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 64 % of theory,

$C_{28}H_{28}N_6O_3$ (496.6)

EKA mass spectrum: $(M+H)^+$ = 497

$(M+H+Na)^{++}$ = 260

$(M+Na)^+$ = 519

$(M+2Na)^{++}$ = 271

Example 138

1-Methyl-2-[N-(4-amidinophenyl)-N-(n-butyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-N-(n-butyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 62 % of theory,

$C_{32}H_{38}N_6O_3$ (554.7)

EKA mass spectrum: $(M+H)^+$ = 555

$(M+H+Na)^{++}$ = 289

$(M+2H)^{++}$ = 278

Example 139

1-Methyl-2-[N-(4-amidino-2-chloro-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-chloro-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 82 % of theory,

$C_{28}H_{29}ClN_6O_3$ (533.1)

EKA mass spectrum: $(M+H)^+$ = 533/5

$(M+H+Na)^{++}$ = 278/9

Example 140

1-Methyl-2-[N-[4-(n-octyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-octyl chloroformate.

Yield: 34 % of theory,

$C_{37}H_{46}N_6O_5$ (654.8)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 19:1)

EKA mass spectrum: $(M+H)^+$ = 655

$(M+H+Na)^{++}$ = 339

$(M+Na)^+$ = 677

Example 141

1-Methyl-2-[N-(4-amidino-2-ethyl-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-ethyl-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 61 % of theory

$C_{30}H_{34}N_6O_3$ (526.6)

EKA mass spectrum: $(M+H)^+$ = 527

$(M+H+Na)^{++}$ = 275

$(M+2H)^{++}$ = 264

Example 142

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-benzylamide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-benzylamide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 63 % of theory,

$C_{24}H_{24}N_6O$ (412.5)

R_f value: 0.76 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 413

Example 143

1-Methyl-2-[N-[4-(N-(2-(2-ethoxyethoxy)ethyloxy)-carbonylamidino)-phenyl]-aminomethyl]-benzimidazol-5-yl-

carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and diethyleneglycolmonoethylether chloroformate.

Yield: 43 % of theory,

$C_{34}H_{41}N_7O_7$ (659.8)

R_f value: 0.56 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 660

$(M+H+Na)^{++}$ = 341.7

Example 144

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 60 % of theory,

$C_{26}H_{30}N_8O_3$ (502.6)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 503

$(M+H+Na)^{++}$ = 263

$(M+2H)^{++}$ = 252

Example 145

3-Methyl-2-[(4-amidinophenyl)-thiomethyl]-imidazo[4,5-b]-pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 1 from 3-methyl-2-[(4-cyanophenyl)thiomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 88 % of theory,

$C_{27}H_{28}N_6O_3S$ (516.63)

R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 517

$(M+H+Na)^{++}$ = 270

Example 146

3-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 1 from 3-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 82 % of theory,

$C_{27}H_{29}N_7O_3$ (499.58)

R_f value: 0.20 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 500

$(M+H+Na)^{++}$ = 261.7

Example 147

3-Methyl-2-[(4-amidinophenyl)-thiomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 2 from 3-methyl-2-[(4-amidinophenyl)-thiomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 88 % of theory,

$C_{25}H_{24}N_6O_3S$ (488.56)

R_f value: 0.21 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 489

$(M+Na)^+$ = 511

Example 148

3-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 2 from 3-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-imidazo[4,5-b]pyridin-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 80 % of theory,

$C_{25}H_{25}N_7O_3$ (471.52)

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 472

$(M+Na)^+$ = 494

$(M+2Na)^{++}$ = 258.6

Example 149

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 1-Methyl-2[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

2.54 g (6,2 mMol) of 3-nitro-4-methylamino-benzenesulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide were hydrogenated at room temperature under 5 bar hydrogen pressure over palladium/charcoal (10%) in a mixture of 75 ml of ethanol and 75 ml of dichloromethane. The resulting crude 3-amino-4-methylamino-benzenesulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide was taken up in 30 ml of phosphorus oxychloride, without purification, then 1.1 g (6,2 mMol) of N-(4-cyanophenyl)-glycine were added and the mixture was refluxed for two hours. After cooling to room temperature the reaction mixture was added to about 70 ml of water with cooling and in this way the excess phosphorus oxychloride was destroyed. The resulting solution was neutralised with solid sodium carbonate and extracted three times with 30 ml of ethyl acetate. After evaporation of the solvent the crude product was purified by column chromatography (100 g silica gel; eluant: cyclohexane/ethyl acetate = 2:3).

Yield: 860 mg (26.8 % of theory),

Melting point: 188-191°C

$C_{27}H_{27}N_5O_3S$ (517.6)

R_f value: 0.52 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 518

$(M+Na)^+$ = 540

b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 87 % of theory,

$C_{27}H_{30}N_6O_4S$ (534.6)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 535

$(M+H+Na)^{++}$ = 279

Example 150

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide, ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 38 % of theory,

$C_{25}H_{30}N_8O_4S$ (538.6)

R_f value: 0.09 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 539

Example 151

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-(2.3-dihydroindol-1-yl-sulphonyl)-benzimidazole-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-(2.3-dihydroindol-1-yl-

sulphonyl)-benzimidazole and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 15 % of theory,
R_f value: 0.36 (silica gel; dichloromethane/methanol = 4:1)
$C_{24}H_{24}N_6O_2S$ (460.6)
EKA mass spectrum: $(M+H)^+$ = 461

Example 152

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazole-5-yl-sulphonic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 24 % of theory,
R_f value: 0.55 (Reverse-Phase RP-18 silica gel; methanol/5% saline solution = 3:2)
$C_{25}H_{26}N_6O_4S$ (506.6)
EKA mass spectrum: $(M+H)^+$ = 507
$(M+Na)^+$ = 529
$(M+2Na)^{++}$ = 276

Example 153

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-(isoindolin-2-yl-sulphonyl)-benzimidazol-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-(isoindolin-2-yl-sulphonyl)-benzimidazole and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 33 % of theory,

R_f value: 0.32 (silica gel; dichloromethane/methanol = 4:1)

$C_{24}H_{24}N_6O_2S$ (460.6)

EKA mass spectrum: $(M+H)^+ = 461$

Example 154

2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a. Ethyl 4-methyl-3-nitro-benzoate

To a solution of 3 ml of concentrated hydrochloric acid and 4 ml of concentrated sulphuric acid, 4.9 g (0.03 mol) of ethyl p-tolylate were added dropwise with stirring at 5°C and stirred for 1 hour whilst cooling in an ice-bath. After heating to ambient temperature the mixture was poured onto ice-water and extracted with ethyl acetate. The organic extracts were washed with sodium hydrogen carbonate solution, dried and evaporated down.

Yield: 5.7 g (90 % of theory),

R_f value: 0.81 (silica gel, ethyl acetate/cyclohexane = 1:1)

b. Methyl 4-(2-dimethylaminovinyl)-3-nitro-benzoate

1.0 g (4.8 mmol) of ethyl 4-methyl-3-nitro-benzoate, 0.74 g (6.2 mmol) of dimethylformamide dimethylacetal and 2 ml of dimethylformamide were heated to 140°C with stirring for 3 hours. Then the solvent was distilled off and the crude product thus obtained was reacted without any further purification.

Yield: 1.2 g (100 % of theory),

R_f value: 0.54 (silica gel, ethyl acetate/cyclohexane = 1:1)

c. Methyl 4-formyl-3-nitro-benzoate

1.2 g (4.8 mmol) of methyl 4-(2-dimethylaminovinyl)-3-nitro-benzoate were dissolved in 120 ml of tetrahydrofuran/water (1:1) and after the addition of 3.0 g

(14.3 mmol) of sodium metaperiodate the mixture was stirred for 20 hours at ambient temperature. The suspension was then diluted with water and methylene chloride and extracted with methylene chloride. The combined organic extracts were washed with sodium hydrogen carbonate solution, dried and evaporated down. The residue was chromatographed on silica gel and eluted with ethyl acetate/cyclohexane (1:3).

Yield: 0.6 g (63 % of theory),

R_f value: 0.63 (silica gel, ethyl acetate/cyclohexane = 1:1)

d. Methyl 3-Amino-4-formyl-benzoate

To a solution of 25 ml of ethanol/glacial acetic acid/water (2:2:1) were added 0.6 g (2.9 mmol) of methyl 4-formyl-3-nitro-benzoate, 1.2 g (21.4 mmol) of iron powder and 0.01 ml of concentrated hydrochloric acid and the mixture was refluxed with stirring for 15 minutes. Then the iron was separated off, the solution was diluted with water and extracted with methylene chloride. The combined organic extracts were washed with water, dried and evaporated down.

Yield: 0.3 g (58 % of theory),

R_f value: 0.74 (silica gel, methylene chloride/methanol = 9.5:0.5)

e. Methyl 3-[3-(4-cyanophenyl)-propionylamino]-4-formyl-benzoate

1.0 g (5.6 mmol) of methyl 3-amino-4-formyl-benzoate and 1.1 g (5.6 mmol) of 4-cyanophenylpropionic acid chloride were dissolved in 50 ml of methylene chloride and after the addition of 0.7 g (5.6 mmol) of N-ethyl-diisopropylamine the mixture was stirred for 24 hours at ambient temperature. Then it was extracted with sodium hydrogen carbonate solution, the combined organic extracts were dried and evaporated down. The residue was chromatographed

on silica gel and eluted with ethyl acetate/cyclohexane (1:3).
Yield: 0.6 g (32 % of theory),
R_f value: 0.60 (silica gel, ethyl acetate/cyclohexane = 1:1)

f. Methyl 2-[2-(4-cyanophenyl)-ethyl]-quinazoline-7-carboxylate

0.6 g (1.8 mmol) of ethyl 3-[3-(4-cyanophenyl)-propionylamino]-4-formyl-benzoate and 10 ml of methanolic ammonia solution were agitated in a pressure vessel for 36 hours. Then the solvent was distilled off, the residue was chromatographed on silica gel and eluted with methylene chloride containing 0 to 1 % methanol.
Yield: 0.35 g (62 % of theory),
R_f value: 0.38 (silica gel, ethyl acetate/cyclohexane = 1:1)

g. 2-[2-(4-Cyanophenyl)-ethyl]-quinazolin-7-carboxylic acid

0.3 g (0.94 mmol) of methyl 2-[2-(4-cyanophenyl)-ethyl]-quinazoline-7-carboxylate were dissolved in 4.7 ml of 1N lithium hydroxide solution and 4 ml of tetrahydrofuran and stirred for 3 hours at ambient temperature. Then 4.7 ml of 1N hydrochloric acid were added and the mixture was stirred for 30 minutes. The product precipitated was suction filtered, washed with water and dried.
Yield: 0.30 g (100 % of theory),
R_f value: 0.1 (silica gel, ethyl acetate/cyclohexane = 1:1)

h. 2-[2-(4-Cyanophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

0.4 g (1.3 mmol) of 2-[2-(4-cyanophenyl)-ethyl]-quinazoline-7-carboxylic acid and 5 ml of thionyl chloride were stirred for 60 minutes at 50°C. Then the thionyl chloride was distilled off, the residue was dissolved in

methylene chloride, mixed with 0.24 g (1.3 mmol) of methyl 3-(N-phenylamino)-propionate and 0.22 ml of (1.3 mmol) of N-ethyldiisopropylamine and stirred for 18 hours at ambient temperature. After evaporation of the solvent *in vacuo* the residue was chromatographed on silica gel and eluted with methylene chloride containing 1 % methanol.

Yield: 230 mg (37 % of theory),

R_f value: 0.64 (silica gel, methylene chloride/methanol = 9:1)

i. 2-[2-(4-Amidinophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

230 mg (0.5 mmol) of 2-[2-(4-cyanophenyl)-ethyl]-quinazolin-7-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were stirred in 30 ml of saturated ethanolic hydrochloric acid for 8 hours at ambient temperature. Then the mixture was evaporated to dryness *in vacuo*, the residue was taken up in 20 ml of ethanol, combined with 0.5 g (5.0 mmol) of ammonium carbonate and stirred overnight at ambient temperature. After evaporation of the solvent the crude product was chromatographed on silica gel and eluted with methylene chloride/ethanol (4:1).

Yield: 100 mg (39 % of theory),

R_f value: 0.5 (silica gel, methylene chloride/ethanol = 4:1)

$C_{29}H_{29}N_5O_3$ (495.59)

Mass spectrum: $(M+H)^+ = 496$

Example 155

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-sulphonic acid-N-(1-methylpyrazol-4-yl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.
Yield: 95 % of theory,
$C_{23}H_{26}N_8O_4S$ (510.6)
R_f value: 0.53 (Reversed Phase silica gel RP-18, methanol + 5% saline solution)
EKA mass spectrum: $(M+H)^+$ = 511
$(M+Na)^+$ = 533
$(M+2Na)^{++}$ = 278

Example 156

1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 3-[(N-tert.Butoxycarbonyl-amino)acetylamino]-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

19.2 g (0.11 mol) of N-tert.butyloxycarbonylglycine were dissolved in 175 ml of dimethylformamide, mixed with 35.2 g (0.11 mol) of O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, 11.0 g of triethylamine and 34.2 g (0.10 mol) of 3-amino-4-methyl-amino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and stirred for 2.5 hours at ambient temperature. Then the reaction solution was mixed with 5 l of ice water and stirred for 2 hours. The grey precipitate formed was filtered off, washed with water, dried and recrystallised from ethyl acetate with the addition of activated charcoal.
Yield: 39.85 g (80 % of theory),

$C_{25}H_{33}N_5O_6$ (499.6)

R_f value: 0.55 (silica gel; methylene chloride/ethanol = 19:1)

b) 1-Methyl-2-(N-tert.butoxycarbonyl-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

10.0 g (0.02 mol) of 3-[(N-tert.butoxycarbonyl-amino)acetylamino]-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide were dissolved in 50 ml of glacial acetic acid and refluxed for one hour. Then the solvent was distilled off, the residue was mixed with ice water and adjusted to pH 8 by the addition of 2N ammonia. After extraction three times with ethyl acetate the combined organic phases were washed with saline solution and dried over sodium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel, eluting first with methylene chloride, then with methylene chloride/ethanol (50:1) and (25:1). The desired fractions were combined and evaporated down.

Yield: 5.85 g (61 % of theory),

$C_{25}H_{31}N_5O_5$ (481.6)

R_f value: 0.70 (silica gel; methylene chloride/ethanol = 9:1)

c) 1-Methyl-2-aminomethyl-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-trifluoracetate

4.81 g (0.10 mol) of 1-methyl-2-(N-tert.butoxycarbonyl-aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide were dissolved in 25 ml of methylene chloride, mixed with 5 ml of trifluoroacetic acid and stirred for 5 hours at ambient temperature. Then the solvent was evaporated off and the residue was stirred with ether. The crystals thus formed were filtered off, washed with ether and dried.

Yield: 3.15 g (68 % of theory),
$C_{20}H_{23}N_5O_3$ (381.4)
R_f value: 0.18 (silica gel; methylene chloride/ethanol = 9:1)

d) 1-Methyl-2-[N-(3-cyano-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

1.5 g (3.25 mmol) of 1-methyl-2-aminomethyl-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-trifluoracetate were stirred into 10 ml of N-ethyl-diisopropylamine and heated to 100°C for 15 minutes. After the addition of 720 mg (5.25 mmol) of 2-chloro-5-cyano-pyridine the reaction mixture was heated to 125°C for 2 hours. After cooling to ambient temperature and stirring with about 20 ml of water, the pH was adjusted to 4 by the addition of 1N hydrochloric acid and the mixture was extracted 3 times with ethyl acetate. The combined organic phases were washed with saline solution and dried over sodium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel, eluting first with methylene chloride, later with methylene chloride/ethanol (25:1) and (19:1). The desired fractions were combined and evaporated down.
Yield: 1.05 g (67 % of theory),
$C_{26}H_{25}N_7O$ (483.6)
Mass spectrum: $(M+H)^+ = 484$

e) 1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride
Prepared analogously to Example 25d from 1-Methyl-2-[N-(3-cyano-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-

amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 38 % of theory,
$C_{28}H_{28}N_8O_3$ (500.6)
Mass spectrum: $(M+H)^+$ = 501

Example 157

1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydroiodide

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a) 4-Nitro-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide

16.7 g (0.1 mol) of 4-nitrobenzoic acid were refluxed in 50 ml of thionyl chloride and 3 drops of dimethylformamide for 1 hour. After the solvent had been distilled off *in vacuo* the crude product was dissolved in 150 ml of tetrahydrofuran and added dropwise to a solution of 18 g (0.1 mol) of N-(2-methoxycarbonylethyl)aniline in 250 ml of tetrahydrofuran and 42 ml 0.3 mol) of triethylamine. After being stirred for one hour at ambient temperature the reaction mixture was diluted with 250 ml of ethyl acetate and washed 2x with 200 ml of 14% saline solution. After the solvent had been distilled off and the residue chromatographed (silica gel; methylene chloride) a yellow oil was obtained which slowly solidified.
Yield: 32.6 g (100 % of theory),
R_f value: 0.37 (silica gel; methylene chloride/methanol = 50:1)

b) 4-Amino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide

22 g (67 mmol) of 4-nitro-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were hydrogenated in 500 ml of methanol with 2 g of 10% palladium on charcoal at 3 bar hydrogen pressure for 3 hours. After filtration and

distillation of the solvent the reaction mixture was washed with 100 ml of ether and the white crystalline product was further reacted directly.

Yield: 18.6 g (94 % of theory),

R_f value: 0.70 (silica gel; methylene chloride/ethanol = 19:1)

c) 2-Methyl-3-thiomethyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

26.8 g (91 mmol) of 4-amino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)amide were dissolved in 500 ml of methylene chloride, cooled to -70°C and mixed within 30 minutes with freshly prepared tert.butylhypochlorite (M. J. Mintz et al., Organic Synthesis, Coll. Vol. 5, page 184). The mixture was stirred for 2 hours at -70°C, then 9.46 g (91 mmol) of methylthioacetone in 40 ml of methylene chloride were added dropwise within 10 minutes and stirring was continued for a further 1.5 hours. Then 12.7 ml (9.1 g, 91 mmol) of triethylamine in 25 ml of methylene chloride were added. The mixture was left for 30 minutes at -78°C and then slowly warmed to ambient temperature overnight. After washing twice with 50 ml of water the organic phase was separated off and dried with sodium sulphate. After removal of the solvent *in vacuo* a white amorphous substance is obtained after purification by chromatography (silica gel; ethyl acetate/petroleum ether = 2:8 to 3:7).

Yield: 24.1 g (69 % of theory),

R_f value: 0.58 (silica gel; ethyl acetate/petroleum ether = 1:1)

$C_{21}H_{22}N_2O_3S$ (382.49)

Mass spectrum: $(M)^+ = 382$

d) 1-tert-Butoxycarbonyl-2-methyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

8.9 g (23 mmol) of 2-Methyl-3-thiomethyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 600 ml of ethanol, mixed with about 150 mg of Raney nickel and stirred for 2 hours at ambient temperature (analogously to P.G. Gassman et al., Organic Synthesis Coll. Vol. 6, page 601). Then the mixture was filtered and the solvent eliminated *in vacuo*. The crude product thus obtained (8 g) was dissolved in 200 ml of absolute tetrahydrofuran, mixed with 150 mg of dimethylaminopyridine and 6.84 g (32 mmol) of di-tert.butyl pyrocarbonate and stirred for 2.5 hours at 50°C. Then the solvent was distilled off *in vacuo* and the crude product was purified by chromatography (silica gel, ethyl acetate/petroleum ether = 1:4).

Yield: 10.0 g (98 % of theory),

R_f value: 0.40 (silica gel; ethyl acetate/petroleum ether =3:7)

e) 2-[N-(4-Cyanophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

3.5 g (8 mmol) of 1-tert.butoxycarbonyl-2-methyl-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 80 ml of carbon tetrachloride, mixed with 1.5 g (8.4 mmol) of N-bromo-succinimide and 20 mg of azobisisobutyronitrile and refluxed for 2.5 hours. Then the still warm solution was filtered, the filtrate obtained was washed with saturated sodium hydrogen carbonate solution and dried with sodium sulphate. After distillation of the solvent the crude product was dissolved in 30 ml of N-ethyl-diisopropylamine, mixed with 1.0 g (8 mmol) of 4-aminobenzonitrile and refluxed for 2.5 hours. The solvent was distilled off *in vacuo* and the residue obtained was purified by chromatography (silica gel; ethyl acetate/petroleum ether = 1:4 to 1:1).

Yield: 1.1 g (30 % of theory),
R_f value: 0.21 (silica gel; ethyl acetate/petroleum ether = 1:1)

f. 1-Methyl-2-[N-(4-thiocarbamoyl-phenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

1.5 g (3.3 mmol) of 2-[N-(4-cyanophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 60 ml of xylene, mixed with 0.45 g (3.3 mmol) of potassium carbonate and 0.5 ml of (3.3 mmol) of methyl p-toluenesulphonate and refluxed for 4 hours. Then the same amounts of potassium carbonate and methyl toluenesulphonate were added a second time and the mixture was refluxed overnight. It was filtered and washed with acetone. After concentration of the filtrate thus obtained, the residue obtained was purified by chromatography (silica gel; ethyl acetate/petroleum ether = 1:4 to 2:3). The N-methylated indole obtained (yield: 0.64 g, 41 % of theory) was dissolved in 20 ml of pyridine and mixed with 0.67 ml (1.37 mmol) of triethylamine. Then hydrogen sulphide gas was introduced into the solution thus obtained. After 4.5 days nitrogen was passed through the reaction solution for 30 minutes, the solvent was distilled off and the residue obtained was purified by chromatography (silica gel; methylene chloride/ethanol 99:1 to 98:2).
Yield: 0.30 g (43 % of theory),
$C_{28}H_{28}N_4O_3S$ (500.62)

EKA mass spectrum: $(M+H)^+$ = 501
$(M+Na)^+$ = 523

g) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide-hydroiodide

0.30 g (0.60 mmol) of 1-methyl-2-[N-(4-thiocarbamoyl)-phenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were dissolved in 20 ml of

acetone together with 0.75 ml (12 mmol) of methyl iodide and stirred for 2 hours at ambient temperature. Then the solvent was distilled off and the crude product was stirred together with 1.0 g of ammonium acetate in 12 ml of ethanol and 5 ml of methylene chloride for 20 hours at 40°C. The solvent was distilled off *in vacuo* and the residue obtained was purified by chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).

Yield: 55 % of theory,

$C_{28}H_{29}N_5O_3$ (483.58)

R_f value: 0.20 (silica gel; methylene chloride/ethanol = 4:1 + 1 drop of acetic acid)

EKA mass spectrum: $(M+H)^+ = 484$

Example 158

1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

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a) Iminoethyl methoxyacetate hydrochloride

A solution of 35.5 g (0.50 mol) of methoxyacetonitrile in 29 ml (23 g, 0.50 mol) of ethanol and 30 ml of absolute diethylether was cooled to 0°C and over 1 hour 22.5 g (0.62 mol) of hydrogen chloride gas was introduced, whilst towards the end of the introduction of gas the reaction product crystallised out. To complete the precipitation 130 ml of diethylether were added and the colourless needles were filtered off.

Yield: 66.4 g (86 % of theory),

Melting point: 117-118°C.

b) 4-Hydroxymethyl-2-methoxymethyl-imidazole

A mixture of 30.6 g (0.20 mol) of iminoethyl methoxyacetate-hydrochloride, 18 g (0.20 mol) of 1.3-dihydroxyacetone and 200 ml of liquid ammonia was heated to 68°C for 3 hours in a stirred autoclave at a pressure of 27

bar (analogously to: P. Dziuron et al. Arch. Pharm. 307, 1974, p.470). Then the ammonia was eliminated and 200 ml of methylene chloride were added. The white precipitate formed was filtered off and washed with methylene chloride. The filtrate was evaporated down and the residue obtained was purified by chromatography (aluminium oxide; methylene chloride/ethanol = 90:10 to 85:15).
Yield: 26.7 g (94 % of theory),
R_f value: 0.43 (silica gel; methylene chloride/ethanol = 9:1)
$C_6H_{10}N_2O_2$ (142.20)
Mass spectrum: $(M)^+ = 142$

c) 4-Hydroxymethyl-2-methoxymethyl-1-methyl-imidazole as a 1:1 mixture with 5-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole

A mixture of 7.1 g (50 mmol) of 4-hydroxymethyl-2-methoxymethylimidazole, 3.0 g (53 mmol) of powdered potassium hydroxide and 3.4 ml (0.55 mmol) of methyl iodide was heated to 50°C in 100 ml of dimethylformamide for 4 hours (analogously to I. Sinclair et al., J. Med. Chem., 29, 1986, 261). Then the solvent was distilled off *in vacuo* and the crude product purified by column chromatography (aluminium oxide; methylene chloride/ethanol = 99:1 to 95:5).
Yield: 6.1 g (78 % of theory; 1:1 mixture of the two regioisomers)
R_f value: 0.32 (silica gel; methylene chloride/ethanol = 19:1)

d) 5-Chloro-4-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole

A 1:1 mixture of 7.7 g (49 mmol) of 4-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole and 5-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole and 7.3 g (55 mmol) of N-chloro-succinimide was heated to 50°C in 48 ml of ethylene glycol monoethylether and 70 ml of dioxan for 10

hours. Then the solvent was distilled off *in vacuo* and the crude product purified by chromatography (silica gel; methylene chloride/ethanol = 99:1 to 90:10) to obtain the isomerically pure title compound.

Yield: 3.4 g (36 % of theory),

R_f value: 0.40 (silica gel; methylene chloride/ethanol = 19:1)

e) 5-chloro-4-formyl-2-methoxymethyl-1-methyl-imidazole

3.4 g (18 mmol) of 5-chloro-4-hydroxymethyl-2-methoxymethyl-1-methyl-imidazole were dissolved in 100 ml of methylene chloride and at two-hour intervals manganese dioxide was added (2 x 6.0 g, a total of 0.14 mol). After 4 hours the inorganic component was filtered off, the solvent was eliminated and the crude product obtained was further reacted without any further purification.

Yield: 3.0 g (89 % of theory),

R_f value: 0.44 (silica gel; methylene chloride/ethanol = 50:1)

f) Ethyl 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylate

To a freshly prepared sodium ethoxide solution (from 391 mg, 17 mMol of sodium) in 15 ml of ethanol were added dropwise 1.9 ml (2.1 g, 17 mmol) of ethyl thioglycolate. After 1 hour stirring at ambient temperature 1.6 g (8.5 mmol) of 5-chloro-4-formyl-2-methoxymethyl-1-methyl-imidazole in 20 ml of absolute ethanol were added and the mixture was heated to 80°C (analogously to B. Iddon et al., J. Chem. Soc. Perkin Trans. I, 1987, 1457). After 5 hours the solvent was distilled off, the residue was taken up in 50 ml of methylene chloride and washed with 20 ml of water. The aqueous phase was washed again with 20 ml of methylene chloride and then the combined organic phases were dried with sodium sulphate. After removal of the solvent *in vacuo* the crude product obtained was purified by column chromatography (aluminium oxide; methylene chloride).

Yield: 1.0 g (46 % of theory),

R_f value: 0.48 (silica gel; methylene chloride/ethanol = 50:1)

$C_{11}H_{14}N_2O_3S$ (254.31)

EKA mass spectrum: $(M+H)^+ = 255$

$(M+Na)^+ = 277$

g) 1-Methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid

To a solution of 0.90 g (3.54 mmol) of ethyl 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylate in 30 ml of ethanol were added dropwise 5 ml of 2 N sodium hydroxide solution and the mixture was stirred for 2 hours at ambient temperature. Then the solvent was distilled off *in vacuo*, the residue was taken up in 5 ml of water and washed with 10 ml of diethylether. The aqueous phase was acidified with 6 ml of 2N hydrochloric acid, cooled to 0°C and the precipitated crystals are filtered off.

Yield: 0.50 g (63% of theory)

R_f value: 0.21 (silica gel; methylene chloride/ethanol = 9:1 + a few drops of acetic acid)

$C_9H_{10}N_2O_3S$ (226.26)

Mass spectrum: $(M)^+ = 226$

h) 1-Methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

A suspension of 0.50 g (2.2 mmol) of 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid in 20 ml of methylene chloride was mixed with 2.0 ml (3.2 g, 27 mmol) of thionyl chloride and refluxed for 60 minutes, during which time the solid gradually dissolved. After distillation of the liquid components the crude product was taken up twice more in methylene chloride. After the solvent had been eliminated once more the crude acid chloride was taken up in 20 ml of tetrahydrofuran and added dropwise to a mixture of 0.42 g (2.3 mmol) of

N-(2-methoxycarbonylethyl)aniline and 0.92 ml (6.6 mmol) of triethylamine in 30 ml of tetrahydrofuran. After 16 hours' stirring at 50°C the solvent was eliminated and the crude product obtained was purified by chromatography (silica gel; methylene chloride/ethanol = 100:1).
Yield: 0.66 g (77% of theory),
R_f value: 0.47 (silica gel; methylene chloride/ethanol = 19:1)

i) 1-Methyl-2-(N-4-cyanophenylaminomethyl)-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

To a solution of 0.73 g (1.88 mmol) of 1-methyl-2-methoxymethyl-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide in 30 ml of methylene chloride were added dropwise at 5°C 2.9 ml (2.9 mmol) of a 1-molar solution of boron tribromide in methylene chloride. After 16 hours' stirring at ambient temperature the mixture was washed with 20 ml of saturated sodium hydrogen carbonate solution, the organic phase was separated off, dried with sodium sulphate and filtered. The filtrate was mixed with 14 ml of N-ethyl-diisopropylamine and 0.43 g (3.64 mmol) of 4-aminobenzonitrile. Then the methylene chloride was distilled off *in vacuo*, the residue obtained was heated to 50°C for 1 hour and then the residual solvent was distilled off *in vacuo*. After chromatography (silica gel; methylene chloride/ethanol = 99:1 to 97:3) a yellow oil was obtained which slowly solidified.
Yield: 0.37 g (42% of theory),
R_f value: 0.29 (silica gel; methylene chloride/ethanol = 50:1 + a few drops of ammonia)

j) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

0.38 g (0.80 mmol) of 1-methyl-2-(N-4-cyanophenylaminomethyl)-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide were stirred in 40 ml of ethanol saturated with hydrogen chloride for 5 hours first at 0°C, then later at ambient temperature until no more starting material could be detected by thin layer chromatography. Then the solvent was distilled off at a maximum 28°C bath temperature, the oily residue was taken up in 40 ml of absolute ethanol and mixed with 1.1 g of ammonium carbonate. After 18 hours the solvent was distilled off *in vacuo* and the crude product was purified by chromatography (silica gel; methylene chloride/ethanol = 9:1 to 4:1).

Yield : 57 % of theory

$C_{26}H_{28}N_6O_3S$ (504.62)

R_f value: 0.21 (silica gel; methylene chloride/ethanol = 4:1 + a few drops of acetic acid)

EKA mass spectrum: $(M+H)^+$ = 505

$(M+H+Na)^{++}$ = 264

Example 159

1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

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Prepared analogously to Example 2 from 1-methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 85 % of theory,

$C_{24}H_{24}N_6O_3S$ (476.56)

R_f value: 0.36 (Reversed Phase silica gel RP-8; methanol + 5 % saline solution)

EKA mass spectrum: $(M+H)^+$ = 477

$(M+Na)^+$ = 499

$(M+2Na)^{++}$ = 250

Example 160

1-Methyl-3-[N-(4-amidinophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

a) 1-Methyl-3-[N-(4-cyanophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide

A solution of 2.5 g (7.6 mmol) of 3-amino-4-methylamino-benzoic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and 2.4 g (9.6 mmol) of ethyl 3-(4-cyanophenyl)thio-2-oxo-propionate were heated to boiling in 50 ml of ethanol for 30 minutes. After removal of the solvent the crude product obtained was purified by chromatography (silica gel; methylene chloride).

Yield: 1.6 g (40 % of theory),

R_f value: 0.63 (silica gel; EtOAc/EtOH/ammonia = 90:10:1)

b) 1-Methyl-3-[N-(4-amidinophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 1 from 1-methyl-3-[N-(4-cyanophenyl)thiomethyl]-quinoxalin-2-on-6-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 23 % of theory,

$C_{28}H_{27}N_5O_4S$ (543.64)

R_f value: 0.25 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 544

$(M+Na)^+$ = 566

Example 161

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

a) 3-Methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

1.4 g (4.6 mmol) of 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid (prepared from 4-bromo-1-(4-cyanophenyl)-1-penten-3-one and methyl 2-aminopyridine-4-carboxylate analogously to Y. Katsura et al. Chem. Pharm. Bull. 1992, 40, 1424-1438) were suspended in 15 ml of thionyl chloride and heated to boiling for 1 hour until fully dissolved. After the thionyl chloride had been distilled off the acid chloride was dissolved in 15 ml of pyridine without any further purification and at 0°C mixed with 1.0 g (5.2 mmol) of N-(2-ethoxycarbonylethyl)-aniline. After 1 hour the solvent was distilled off, the residue was taken up in 30 ml of methylene chloride, washed with 15 ml of 1N hydrochloric acid and dried with sodium sulphate. After distillation of the solvent and chromatography (silica gel; methylene chloride/ethanol = 0 to 2 %) a brown oil was obtained.

Yield: 1.48 g (64 % of theory),

R_f value: 0.73 (silica gel; ethyl acetate/ethanol/ammonia = 90:10:1)

b) 3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 62 % of theory,

$C_{29}H_{31}N_5O_3$ (497.60)

R_f value: 0.23 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 498

Example 162

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 2 from 3-methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 92 % of theory,

$C_{27}H_{27}N_5O_3$ (469.55)

R_f value: 0.19 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 470

$(M+Na)^+$ = 492

$(M+2H)^{++}$ = 235.7

$(M+H+Na)^{++}$ = 246.7

$(M+2Na)^{++}$ = 257.7

Example 163

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-ethoxycarbonylethyl-N-methyl)-2-aminoethyl]-amide-dihydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-ethoxycarbonylethyl-N-methyl)-2-aminoethyl]-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 80 % of theory,

$C_{31}H_{37}N_7O_3$ (555.7)

R_f value: 0.24 (silica gel; dichloromethane/methanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 556

$(M+H+Na)^{++}$ = 289.8

$(M+2H)^{++}$ = 278.8

Example 164

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide-hydrochloride

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-ethoxycarbonylethyl-N-methyl)-2-aminoethyl]-amide-dihydrochloride and sodium hydroxide solution.

Yield: 79 % of theory,

$C_{29}H_{33}N_7O_3$ (527.6)

R_f value: 0.43 (Reversed Phase silica gel RP-18; methanol/5% aqueous saline solution = 6:4)

EKA mass spectrum: $(M+H)^+$ = 528

$(M+H+Na)^{++}$ = 275.6

$(M+2H)^{++}$ = 264.6

Example 165

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxy-n-propyl)-amide-hydrochloride

---

Prepared from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide-hydrochloride by hydrogenation over

palladium/charcoal (10%) at 5 bar hydrogen pressure and at ambient temperature.

Yield: 61 % of theory,

$C_{26}H_{28}N_6O_2$ (456.6)

R_f value: 0.70 (Reversed Phase silica gel RP-18; methanol/5% aqueous saline solution = 9:1)

EKA mass spectrum: $(M+H)^+$ = 457

$(M+H+Na)^{++}$ = 240

Example 166

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and sodium hydroxide solution.

Yield: 97 % of theory,

$C_{32}H_{37}N_7O_5$ (599.7)

R_f value: 0.22 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 600

$(M+H+Na)^{++}$ = 311.7

$(M+2H)^{++}$ = 300.8

$(M+2Na)^{++}$ = 322.8

Example 167

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxy-n-propyl)-amide

---

Prepared analogously to Example 165 from 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-

benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide by catalytic debenzylation.
Yield: 26 % of theory,
$C_{33}H_{40}N_6O_4$ (584.7)
R_f value: 0.39 (silica gel; dichloromethane/ethanol = 9:1)
EKA mass spectrum: $(M+H)^+$ = 585
$(M+H+Na)^{++}$ = 304
$(M+Na)^+$ = 607

Example 168

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 42 % of theory,
$C_{28}H_{29}FN_6O_3$ (516.6)
R_f value: 0.31 (silica gel; dichloromethane/methanol = 5:1)
EKA mass spectrum: $(M+H)^+$ = 517
$(M+H+Na)^{++}$ = 270

Example 169

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide and

ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 90 % of theory,

$C_{28}H_{29}FN_6O_3$ (516.6)

R_f value: 0.29 (silica gel; dichloromethane/methanol = 5:1)

EKA mass spectrum: $(M+H)^+$ = 517

$(M+H+Na)^{++}$ = 270

Example 170

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 97 % of theory,

$C_{26}H_{25}FN_6O_3$ (488.5)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 489

$(M+Na)^+$ = 511

$(M+2Na)^{++}$ = 267

Example 171

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 89 % of theory,

$C_{26}H_{25}FN_6O_3$ (488.5)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 489

$(M+Na)^+$ = 511

$(M+2Na)^{++}$ = 267

Example 172

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 89 % of theory,

$C_{29}H_{32}N_6O_4$ (528.6)

R_f value: 0.13 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 529

$(M+H+Na)^{++}$ = 276

$(M+2H)^{++}$ = 265

Example 173

1-Methyl-2-[N-[4-(N-4-ethylbenzoylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and 4-ethylbenzoylchloride.

Yield: 64 % of theory,

$C_{36}H_{37}N_7O_4$ (631.7)

R_f value: 0.78 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 632

$(M+H+Na)^{++}$ = 327.8

$(M+Na)^+$ = 654

Example 174

1-Methyl-2-[N-[4-(N-benzyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and benzyl chloroformate.

Yield: 64 % of theory,

$C_{35}H_{35}N_7O_5$ (633.6)

R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 634

$(M+H+Na)^{++}$ = 328.8

$(M+Na)^+$ = 656

Example 175

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 71 % of theory,

$C_{27}H_{28}N_6O_4$ (500.6)

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 501

$(M+Na)^+$ = 523

$(M+2Na)^{++}$ = 273

Example 176

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(4-cyano-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 67 % of theory,

$C_{28}H_{31}N_7O_4$ (529.6)

R_f value: 0.16 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 530

Example 177

1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 78 % of theory,

$C_{26}H_{27}N_7O_4$ (501.6)

R_f value: 0.12 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 502

Example 178

1-Methyl-2-[N-[4-(N-benzyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 104 from 1-methyl-2-[N-[4-(N-benzyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and sodium hydroxide solution.
Yield: 62 % of theory,
$C_{33}H_{31}N_7O_5$ (605.7)
R_f value: 0.26 (silica gel; dichloromethane/methanol = 9:1)

EKA mass spectrum:

$(M+H)^+$	= 606
$(M+Na)^+$	= 628
$(M-H+2Na)^+$	= 650
$(M+2H)^{++}$	= 303.8
$(M+H+Na)^{++}$	= 314.8
$(M+2Na)^{++}$	= 325.7

Example 179

1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide-hydrochloride

---

Prepared analogously to Example 25 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.
Yield: 61 % of theory,
$C_{33}H_{34}N_6O_2$ (546.7)
R_f value: 0.19 (silica gel; dichloromethane/ethanol = 4:1)

EKA mass spectrum: $(M+H)^+$ = 547

$(M+H+Na)^{++}$ = 285

Example 180

1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-benzyloxy-n-propyl)-amide-hydrochloride and n-hexyl chloroformate.

Yield: 73 % of theory,

$C_{40}H_{46}N_6O_4$ (674.9)

R_f value: 0.46 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 675

$(M+H+Na)^{++}$ = 349

$(M+Na)^+$ = 697

$(M+K)^+$ = 713

Example 181

3-Methyl-2-[2-(4-amidinophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 1 from 3-methyl-2-[2-(4-cyanophenyl)ethyl]-imidazo[1.2-a]pyridin-7-yl-carboxylic acid-N-(2-pyridyl)-N-(2-methoxycarbonylethyl)-amide-hydrochloride and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 53 % of theory,

$C_{28}H_{30}N_6O_3$ (498.59)

R_f value: 0.42 (silica gel; ethyl acetate/ethanol/ammonia = 50:45:5)

EKA mass spectrum: $(M+H)^+$ = 499

$(M+2Na)^{++}$ = 272

$(M+H+Na)^{++}$ = 261

$(M+2H)^{++}$ = 250

Example 182

1-Methyl-2-[N-(3-amidino-pyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(3-cyanopyridin-6-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide and sodium hydroxide solution.

Yield: 40 % of theory,

$C_{24}H_{24}N_8O_3$ (472.9)

R_f value: 0.67 (Reversed Phase silica gel RP-8; methanol/5% saline solution = 1:1)

EKA mass spectrum: $(M+H)^+$ = 473

Example 183

1-Methyl-2-[N-[4-(N-hydroxylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methansulphonylaminocarbonyl)-ethyl]-amide

---

a. 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methanesulphonylaminocarbonyl)-ethyl]-amide

2.0 g (4.5 mmol) of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide and 0.73 g (4.7 mmol) of carbonyldiimidazole were dissolved in 80 ml of tetrahydrofuran and 5 ml of dimethylformamide and stirred for 30 minutes at ambient temperature and for 2 hours at 90°C. In parallel 0.55 g (5.8 mmol) of

methansulphonic acid amide and 0.28 g (5.8 mmol) of sodium hydride were suspended in 15 ml of dimethylformamide and stirred for 2 hours at ambient temperature. Then this suspension was added at ambient temperature to the tetrahydrofuran solution. After 12 hours at ambient temperature 50 ml of water were added and the pH value was adjusted to 6.8. The solution was extracted 4x with methylene chloride, the combined organic phases were dried over sodium sulphate and evaporated down. The crude product was chromatographed on silica gel (methylene chloride/ethanol (40:1)). The desired fractions were combined and evaporated down. Yield: 1.05 g (44 % of theory),

$C_{26}H_{25}N_7O_4S$ (531.6)

R_f value: 0.72 (silica gel; dichloromethane/methanol = 9:1)

b. 1-Methyl-2-[N-[4-(N-hydroxylamidino)phenyl]-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methansulphonylaminocarbonyl)-ethyl]-amide

Prepared analogously to Example 96 from 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-[2-(methanesulphonylaminocarbonyl)-ethyl]-amide and hydroxylamine.

Yield: 27% of theory,

$C_{26}H_{28}N_8O_5S$ (564.6)

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 7:3 + 1% glacial acetic acid)

EKA mass spectrum: $(M+H)^+ = 565$

$(M+Na)^+ = 587$

Example 184

1-Methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

Prepared analogously to Example 25d from 1-methyl-2-[N-(5-cyano-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: % of theory,

$C_{24}H_{26}N_8O_3S$ (506.6)

R_f value: (silica gel; dichloromethane/methanol = 4:1)

Example 185

1-Methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

Prepared analogously to Example 26 from 1-methyl-2-[N-(5-amidino-thiazol-2-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: % of theory,

$C_{22}H_{22}N_8O_3S$ (478.5)

R_f value: (silica gel; dichloromethane/methanol = 4:1)

Example 186

1-Methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride

---

Prepared analogously to Example 25d from 1-methyl-2-[N-(2-cyano-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and ethanolic hydrochloric acid, ethanol and ammonium carbonate.

Yield: 19 % of theory,

$C_{25}H_{27}N_9O_3$ (501.6)

R_f value: 0.28 (silica gel; dichloromethane/methanol = 4:1 + 1% glacial acetic acid)

EKA mass spectrum: $(M+H)^+$ = 502

$(M+H+Na)^+$ = 262.5

Example 187

1-Methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide

---

Prepared analogously to Example 26 from 1-methyl-2-[N-(2-amidino-pyrazin-5-yl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and sodium hydroxide solution.

Yield: 11 % of theory,

$C_{23}H_{23}N_9O_3$ (473.5)

R_f value: 0.55 (Reversed Phase silica gel RP-8; 5% saline solution/methanol = 6:4)

EKA mass spectrum: $(M+H)^+$ = 474

$(M+H+Na)^+$ = 496.6

Example 188

1-Methyl-2-[2-[4-(N-n-hexyloxycarbonylamidino)phenyl]-ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[2-(4-amidinophenyl)-ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)-ethyl]-amide and n-hexyl chloroformate.

Yield: % of theory,

$C_{34}H_{39}N_9O_3$ (621.7)

R_f value: (silica gel; dichloromethane/methanol = 4:1)

Example 189

1-Methyl-2-[N-(2-methoxy-4-n-pentoxycarbonylamidino-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate.

Yield: 53 % of theory,

$C_{35}H_{42}N_6O_6$ (642.7)

R_f value: 0.54 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 643

$(M+H+Na)^{++}$ = 333.4

Example 190

1-Methyl-2-[N-(4-n-heptyloxycarbonylamidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate.

Yield: 68 % of theory,

$C_{37}H_{46}N_6O_6$ (670.8)

R_f value: 0.56 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 671

$(M+H+Na)^{++}$ = 347.4

Example 191

1-Methyl-2-[N-(4-ethoxycarbonylamidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and ethyl chloroformate.

Yield: 43 % of theory,

$C_{31}H_{35}N_7O_6$ (601.7)

R_f value: 0.44 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 602

$(M+H+Na)^{++}$ = 312.8

Example 192

1-Methyl-2-[N-(2-methoxy-4-n-pentoxycarbonylamidino-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-pentyl chloroformate.

Yield: 72 % of theory,

$C_{34}H_{41}N_7O_6$ (643.7)

R_f value: 0.49 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 644

$(M+H+Na)^{++}$ = 333.9

Example 193

1-Methyl-2-[N-(2-methoxy-4-n-heptyloxycarbonylamidino-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

---

Prepared analogously to Example 90 from 1-methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide-hydrochloride and n-heptyl chloroformate.

Yield: 55 % of theory,

$C_{36}H_{45}N_7O_6$ (671.8)

R_f value: 0.54 (silica gel; dichloromethane/ethanol = 9:1)

EKA mass spectrum: $(M+H)^+$ = 672

$(M+H+Na)^{++}$ = 347.9

Example 194

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

Active substance	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:
Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 195

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

Active substance	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:
Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use, the product is dissolved in water for injections.

Example 196

Tablet containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:
(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 9 mm.

Example 197

Tablet containing 350 mg of active substance

Preparation:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 12 mm.

Example 198

Capsules containing 50 mg of active substance

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

Example 199

Capsules containing 350 mg of active substance

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Powdered lactose	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Example 200

Suppositories containing 100 mg of active substance

1 suppository contains:

Active substance	100.0 mg
Polyethyleneglycol (M.W. 1500)	600.0 mg
Polyethyleneglycol (M.W. 6000)	460.0 mg
Polyethylenesorbitan monostearate	840.0 mg
	2,000.0 mg

What is claimed is:

1. A compound of the formula I

$$R_a - A - Het - B - Ar - E \qquad (I)$$

wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, wherein a methylene group, linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-6}-alkyl group,

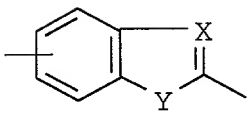
E denotes a cyano or $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3}-alkyl group or a group which may be cleaved *in vivo*,

Ar denotes a phenylene or naphthylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

Het denotes a bicyclic heterocycle of formula



, wherein

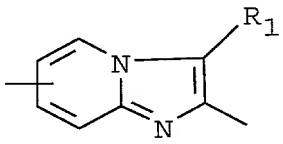
X is a nitrogen atom and

Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R_1, wherein R_1 is as hereinbefore defined, and

Y denotes a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group,

or Het denotes a group of the formula



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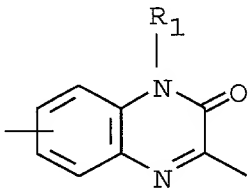

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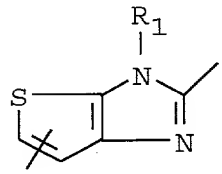

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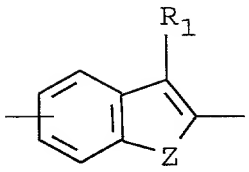

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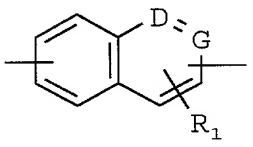

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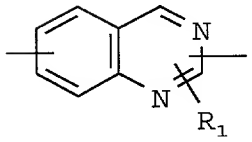


, wherein

R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom,

one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or an R_2NR_3- group wherein

R_2 denotes a C_{1-4}-alkyl group, which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C_{2-4}-alkyl group substituted by a hydroxy, phenyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position relative to the adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a C_{1-3}-alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, a C_{3-6}-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3- group, a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, thienyl or imidazolyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or C_{1-4}-alkoxycarbonyl group, onto which a phenyl ring may additionally be fused,

or a tautomer or salt thereof.

2. A compound of the formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno

moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group, in which a methylene group, linked either to the group Het or Ar, may be replaced by an oxygen or sulphur atom or by a sulphinyl, sulphonyl, carbonyl or $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-5}-alkyl group,

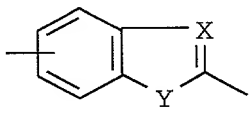
E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy group, a C_{1-3}-alkyl group or a group which may be cleaved *in vivo*,

Ar denotes a phenylene group optionally substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

Het denotes a bicyclic heterocycle of formula



, wherein

X is a nitrogen atom and

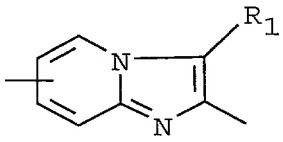
Y is an oxygen or sulphur atom or a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group, whilst additionally one or two non-angular methyne groups in the phenyl moiety of the

above-mentioned bicyclic heterocycle may each be replaced by a nitrogen atom,

or X denotes a methyne group optionally substituted by the group R_1, wherein R_1 is as hereinbefore defined, and

Y denotes a nitrogen atom optionally substituted by a C_{1-6}-alkyl or C_{3-7}-cycloalkyl group,

or Het denotes a group of the formulae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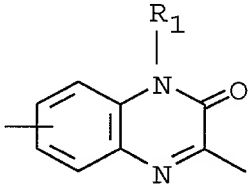
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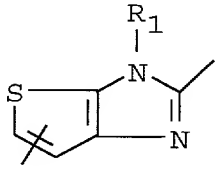
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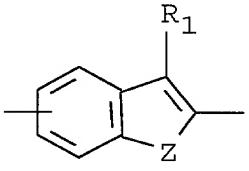
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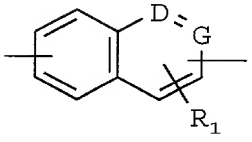
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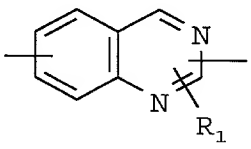

wherein

R_1 is as hereinbefore defined,

Z denotes an oxygen or sulphur atom

one of the groups D or G denotes a nitrogen atom and the other group D or G denotes a methyne group,

and R_a denotes a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, wherein the C_{1-3}-alkyl group may additionally be substituted by a carboxyl group or by a group which may be converted *in vivo* into a carboxy group,

or a R_2NR_3- group wherein

R_2 denotes a C_{1-4}-alkyl group, which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, trifluorosulphonylamino, trifluorosulphonylaminocarbonyl or 1H-tetrazolyl group,

a C_{2-4}-alkyl group substituted by a hydroxy, phenyl-C_{1-3}-alkoxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position relative to the adjacent nitrogen atom may not be substituted, or

a piperidinyl group optionally substituted by a C_{1-3}-alkyl group and

R_3 denotes a hydrogen atom, a C_{1-6}-alkyl group, a C_{3-7}-cycloalkyl group optionally substituted by a C_{1-3}-alkyl group, a C_{3-6}-alkenyl or alkynyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3- group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl or C_{1-3}-alkoxy group, a benzyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, thienyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, imidazolyl or piperidinyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxymethyl or C_{1-4}-alkoxycarbonyl group, onto which additionally a phenyl ring may be fused,

or a tautomer or salt thereof.

3. A compound of the formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido, pyrimido, pyrazino, pyridazino or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a C_{1-4}-alkyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b denotes a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, phenyl-C_{1-3}-alkoxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or pyridinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a C_{1-3}-alkyl-sulfonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group or it denotes a 2,5-thienylene group,

Het denotes a 1-(C_{1-3}-alkyl)-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-(C_{1-3}-alkyl)-2,5-indolylene, 1-(C_{1-3}-alkyl)-2,5-imidazo[4,5-b]pyridinylene, 3-(C_{1-3}-alkyl)-2,7-imidazo[1,2-a]pyridinylene or 1-(C_{1-3}-alkyl)-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R_2NR_3- group wherein

R_2 is a C_{1-4}-alkyl group substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, C_{1-3}-alkylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-4}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon

atom in the α-position to the adjacent nitrogen atom may not be substituted,

R_3 denotes a C_{3-7}-cycloalkyl group, a propargyl group, wherein the unsaturated part may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally substituted by a fluorine or chlorine atom, or by a methyl or methoxy group, a pyrazolyl, pyridazolyl or pyridinyl group optionally substituted by a methyl group or

R_2 and R_3 together with the nitrogen atom between them denote a 5- to 7-membered cycloalkyleneimino group, optionally substituted by a carboxy or C_{1-4}-alkoxycarbonyl group, to which a phenyl ring may additionally be fused,

or a tautomer or salt thereof.

4. A compound of the formula I according to claim 1, wherein

A denotes a carbonyl or sulphonyl group linked to the benzo, pyrido or thieno moiety of the group Het, whilst moreover the abovementioned moieties may not contain an R_1 group,

B denotes an ethylene group in which the methylene group linked to the group Ar may be replaced by an oxygen or sulphur atom or by an $-NR_1-$ group, wherein

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group, wherein

R_b denotes a hydrogen atom or a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkylbenzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a C_{1-3}-alkylsulphonyl or 2-(C_{1-3}-alkoxy)-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a chlorine atom or by a methyl, ethyl or methoxy group, or it denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 1-cyclopropyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene, 1-methyl-2,5-imidazo[4,5-b]pyridinylene, 3-methyl-2,7-imidazo[1,2-a]pyridinylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes a R_2NR_3- group wherein

R_2 denotes a C_{1-3}-alkyl group which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulphonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-3}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted, and

R_3 denotes a propargyl group, wherein the unsaturated moiety may not be linked directly to the nitrogen atom of the R_2NR_3 group, a phenyl group optionally

substituted by a fluorine or chlorine atom, or by a methyl or methoxy group or it denotes a pyridinyl group,

or a tautomer or salt thereof.

5. A compound of the formula I according to claim 1, wherein

A denotes a carbonyl group linked to the benzo or thieno moiety of the group Het,

B denotes an ethylene group wherein the methylene group attached to the group Ar may be replaced by an $-NR_1$ group, whilst

R_1 denotes a hydrogen atom or a methyl group,

E denotes an $R_bNH-C(=NH)-$ group wherein

R_b is a hydrogen atom, a hydroxy, C_{1-9}-alkoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, benzoyl, p-C_{1-3}-alkyl-benzoyl or nicotinoyl group, whilst the ethoxy moiety in the 2-position of the abovementioned C_{1-9}-alkoxycarbonyl group may additionally be substituted by a methylsulfonyl or 2-ethoxy-ethyl group,

Ar denotes a 1,4-phenylene group optionally substituted by a methoxy group or it denotes a 2,5-thienylene group,

Het denotes a 1-methyl-2,5-benzimidazolylene, 2,5-benzothiazolylene, 1-methyl-2,5-indolylene or 1-methyl-2,5-thieno[2,3-d]imidazolylene group and

R_a denotes an R_2NR_3- group wherein

R_2 denotes a C_{1-3}-alkyl group which may be substituted by a carboxy, C_{1-6}-alkyloxycarbonyl, benzyloxycarbonyl, methylsulfonylaminocarbonyl or 1H-tetrazol-5-yl group,

a C_{2-3}-alkyl group substituted by a hydroxy, benzyloxy, carboxy-C_{1-3}-alkylamino, C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino, N-(C_{1-3}-alkyl)-carboxy-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkoxycarbonyl-C_{1-3}-alkylamino group, whilst in the abovementioned groups the carbon atom in the α-position to the adjacent nitrogen atom may not be substituted, and

R_3 denotes a phenyl group optionally substituted by a fluorine atom, or it denotes a 2-pyridinyl group,

or a tautomer or salt thereof.

6. A compound selected from the group consisting of:

(a) 2-[N-(4-amidinophenyl)-aminomethyl]-benzthiazole-5-carboxylic acid-N-phenyl-N-(2-carboxyethyl)-amide,

(b) 2-[N-(4-midinophenyl)-N-methyl-aminomethyl]-benzthiazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(c) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(d) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(3-hydroxycarbonylpropyl)-amide,

(e) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,

(f) 1-Methyl-2-[2-(2-amidinothiophen-5-yl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(g) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(h) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(i) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(j) 1-Methyl-2-[2-(4-amidinophenyl)ethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,

(k) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[2-(1H-tetrazol-5-yl)ethyl]-amide,

(l) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(m) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(n) 1-Methyl-2-[N-(4-amidinophenyl)-N-methyl-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(o) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-[(N-hydroxycarbonylethyl-N-methyl)-2-aminoethyl]-amide,

(p) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(3-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,

(q) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(4-fluorophenyl)-N-(2-hydroxycarbonylethyl)-amide,

(r) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(s) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide,

(t) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-indol-5-yl-carboxylic acid-N-phenyl-N-(2-methoxycarbonylethyl)-amide and

(u) 1-Methyl-2-[N-(4-amidinophenyl)aminomethyl]-thieno[2.3-d]imidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

or a prodrug, double prodrug or salt thereof.

7. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide, or a prodrug, double prodrug or salt thereof.

8. 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide or a prodrug, double prodrug or salt thereof.

9. 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-hydroxycarbonylethyl)-amide, or a prodrug, double prodrug or salt thereof.

10. 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide.

11. A physiologically acceptable salt of a compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 wherein E denotes an $R_bNH-C(=NH)-$ group.

12. A pharmaceutical composition containing a compound according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

13. A method for preventing or treating venous and arterial thrombotic disease which comprises administering an antithrombotic amount of a compound according claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt thereof.

14. The method of claim 13 wherein said thrombotic disease is selected from the group consisting of deep leg vein thrombosis, reocclusion after a bypass operation or angioplasty (PT(C)A), occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular coagulation, coronary thrombosis, stroke, and the occlusion of a shunt or stent.

15. A method for providing antithrombotic support in thrombolytic treatment utilizing rt-PA or streptokinase, which comprises administering a therapeutically effective amount of a compound according claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt thereof.

16. A method for preventing metastasis or the growth of clot-dependent tumours, which comprises administering a therapeutically effective amount of a compound according claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt thereof.

17. A method for treating or preventing fibrin-dependent inflammatory processes, which comprises administering a therapeutically effective amount of a compound according claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, wherein E denotes an $R_bNH-C(=NH)-$ group, or a physiologically acceptable salt thereof.

Abstract

New disubstituted bicyclic heterocycles of general formula

$$R_a - A - Het - B - Ar - E \qquad (I)$$

Compounds of the above general formula I, wherein E denotes an $R_bNH-C(=NH)-$ group, have valuable pharmacological properties, particularly a thrombin-inhibiting effect and the effect of prolonging thrombin time, and those wherein E denotes a cyano group, are valuable intermediates for preparing the other compounds of general formula I. Exemplary compounds of formula I are:

(a) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-phenyl-N-(2-hydroxycarbonylethyl)-amide,

(b) 1-Methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide,

(c) 1-Methyl-2-[N-(4-amidino-2-methoxy-phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(hydroxycarbonylmethyl)-amide, and

(d) 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl) amide.

PTO/SB/01 (8-96) SUBSTITUTE

# DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION	Attorney Docket Number	**5/1213**
	First Named Inventor	**Hauel, Norbert; et al**
	COMPLETE IF KNOWN	
	Application Number	**To Be Assigned**
☒ Declaration Submitted with Initial Filing ☐ Declaration Submitted after Initial Filing	Filing Date	
	Group Art Unit	
	Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

DISUBSTITUTED BICYCLIC HETEROCYCLES, THE PREPARATION AND THE USE THEREOF AS PHARMACEUTICAL COMPOSITIONS

the specification of which

☒ is attached hereto

or

☐ was filed on as United States Application Number or PCT International Application Number

and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations , § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119 (a)-(d) or § 365(b) of any foreign application(s) or inventors certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached? Yes	No
197 06 229.6	**DE**	**02/18/97**	☐	☐	☒
197 51 939.3	**DE**	**11/24/97**	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto.

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date	
60/044,421	**04/29/97**	☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.

PTO/SB/01 (8-96) SUBSTITUTE

DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §356(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. PARENT APPLICATION NUMBER	PCT PARENT NUMBER	PARENT FILING DATE	PARENT PATENT NUMBER (if applicable)

☐ **Additional U.S. or PCT international application numbers are listed on a supplemental sheet attached hereto.**

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

NAME	REGISTRATION NUMBER	NAME	REGISTRATION NUMBER
Robert P. Raymond	**25,089**	**Alan R. Stempel**	**28,991**
Mary-Ellen M. Devlin	**27,928**		

☐ **Additional registered practitioner(s) are listed on a supplemental sheet attached hereto.**

Direct all correspondence to:

Name	**Robert P. Raymond**				
Address	**Boehringer Ingelheim Corporation**				
Address	**900 Ridgebury Road, P.O. Box 368**				
City	**Ridgefield**	State	**Connecticut**	Zip	**06877**
Country	**USA**	Telephone	**203-798-9988**	Fax	**203-791-6183**

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

Given Name	**Norbert**	Middle Initial		Family Name	**Hauel**	Suffix e.g. Jr.	
Inventor's Signature	Norbert Hauel			Date	10/2/98		
Residence: City	**Schemmerhofen**	State		Country	**Germany**	Citizenship	**DE**
Post Office Address	**Marderweg 12**						
Post Office Address							
City	**Schemmerhofen**	State		Zip	**D-88433**	Country	**Germany**

☒ **Additional inventors are being listed on a supplemental sheet(s) attached hereto.**

DECLARATION — ADDITIONAL INVENTOR(S) Supplemental Sheet

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Henning		Priepke	

Inventor's Signature: K. Priepke — Date: 9/2/98

Residence: City: Warthausen — State: — Country: Germany — Citizenship: DE

Post Office Address: Birkenharder Strasse 11

Post Office Address:

City: Warthausen — State: — Zip: D-88447 — Country: Germany

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Uwe		Ries	

Inventor's Signature: U. Ries — Date: 8/2/98

Residence: City: Biberach — State: — Country: Germany — Citizenship: DE

Post Office Address: Tannenstrasse 3

Post Office Address:

City: Biberach — State: — Zip: D-88400 — Country: Germany

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Jean Marie		Stassen	

Inventor's Signature: [signature] — Date: 10/2/98

Residence: City: Warthausen — State: — Country: Germany — Citizenship: BE

Post Office Address: Berggrubenweg 11

Post Office Address:

City: Warthausen — State: — Zip: D-88447 — Country: Germany

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	Middle Initial	Family Name	Suffix e.g. Jr.
Wolfgang		Wienen	

Inventor's Signature: Wolfgang Wienen — Date: 10/2/98

Residence: City: Biberach — State: — Country: Germany — Citizenship: DE

Post Office Address: Kirschenweg 27

Post Office Address:

City: Biberach — State: — Zip: D-88400 — Country: Germany

☐ Additional inventors are being listed on a supplemental sheet(s) attached hereto.